8-10-11

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**Express Mail No. EB 132595697 US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 6,538,151

**Attorney Docket No.:** 598527-999029

**Issued:** March 25, 2003

**Inventors:** Meisel *et al.*

**Assignee:** Valeant Pharmaceuticals North America

**For:** Modifications of 2-Amino-4-(4-Fluorobenzylamino)-1-Ethoxycarbonylaminobenzene, and Processes for Their Preparation

"EXPRESS MAIL" MAILING LABEL NUMBER: EB 132595697 US
DATE OF DEPOSIT: August 8, 2011
I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

David A. Gay

**MAIL STOP PATENT EXTENSION**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**FEE TRANSMITTAL LETTER**
**FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156**

Sir:

Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 6,538,151, accompanied by two additional copies. The undersigned attorney for Applicant hereby states that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

| | |
|---|---|
| Exhibit A | U.S. Patent No. 6,538,151 |
| Exhibit B | Assignment Recordations & Assignments |
| Exhibit C | Approved Product Label |
| Exhibit D | FDA Approval Letter |
| Exhibit E | Maintenance Fee Payment Record |

| | |
|---|---|
| Exhibit F | Excerpt from Drug Substance Development Report, Section 3.2.S.2.6 |
| Exhibit G | Log of Significant Regulatory Activities in Connection with POTIGA™ IND and NDA |

Please charge the required fee estimated to be $1,120.00 to Jones Day Deposit Account No. 50-3013. The Director is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: August 8, 2011

39,200
David A. Gay (Reg. No.)

**JONES DAY**
222 East 41st Street
New York, NY 10017
(212) 326-3939

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 6,538,151 **Attorney Docket No.:** 598527-999029

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David A. Gay

**MAIL STOP PATENT EXTENSION**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

08/10/2011 MBLANCO 00000029 503013 6538151
01 FC:1457 1120.00 DA

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156**

Sir:

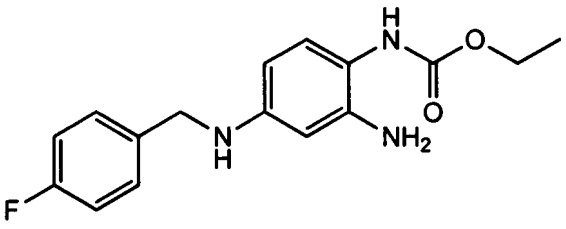
In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Valeant Pharmaceuticals North America, through the undersigned, represents that it is the owner of record of United States Patent No. 6,538,151 ("the '151 patent"), attached hereto as Exhibit A, and hereby requests an extension of the patent term thereof. A copy of the assignments and assignment recordations from the United States Patent and Trademark Office ("USPTO"), which shows the chain of title for the '151 patent, and confirming that all right, title, and interest resides in Valeant Pharmaceuticals North America, is attached hereto as Exhibit B. Specifically, the attached assignments are recorded at: Reel 009562, Frame 0753 (assignment from inventors from ASTA Medica Aktiengesellschaft); Reel 013411, Frame 0778 (name change from ASTA

Medica AG to Viatris Gmbh & Co. KG); Reel 015190, Frame 0936 (assignment from Viatris Gmbh & Co. KG to XCEL Pharmaceuticals, Inc.); and Reel 021109, Frame 0083 (name change from XCEL Pharmaceuticals, Inc. to Valeant Pharmaceuticals North America).

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740. The sections of this application are numbered in a manner corresponding with the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a) and follow the format set forth therein.

***(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics."***

The approved product is POTIGA™, the active ingredient of which is ezogabine. A chemical name of ezogabine is N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester, and the structure is shown as below:




Ezogabine is also known as "retigabine." The molecular weight of ezogabine is about 303.3 and its empirical formula is $C_{16}H_{18}FN_3O_2$. (*See* Product Label at Exhibit C, page 11, lines 29-30).

As currently approved, POTIGA™ is indicated for adjunctive treatment of partial-onset seizures in patients aged 18 years and older. (*See* Product Label at Exhibit C, page 2, lines 3-4). Currently, the approved product is available in the form of tablets having 50 mg, 200 mg, 300 mg or 400 mg strength, for oral administration. (*See* Product Label at Exhibit C, page 2 ($2^{nd}$)[1], lines 9-12).

[1] The approved product label, as currently available from the FDA source, erroneously duplicates page number "2." This refers to the second "page 2" in the currently available product label.

***(2) "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred."***

POTIGA™ was subject to regulatory review for an investigational new drug application ("IND") and a new drug application ("NDA") under section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355 ("FFDCA"). Section 505(b) of the FFDCA, 21 U.S.C. §355(b), authorizes the filing of an NDA for a new drug. The Food and Drug Administration ("FDA") subsequently approved the POTIGA™ NDA (22-345) under the authority granted by section 505(c) of the FFDCA, 21 U.S.C. § 355(c).

***(3) "An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred."***

POTIGA™ received permission for commercial marketing or use by the FDA pursuant to section 505(b) of the FFDCA, 21 U.S.C. § 355(b), on June 10, 2011. Copies of the Product Label and FDA Approval Letter are attached as Exhibits C and D, respectively.

***(4) "In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum- Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved."***

The active ingredient in POTIGA™ is ezogabine. Ezogabine has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

***(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted."***

This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), the last day for said submission being August 9, 2011.

***(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration."***

The complete identification of the patent for which extension is sought is as follows:

| | |
|---|---|
| Inventors: | Peter Meisel; Karl-Friedrich Landgraf; Jürgen Schäfer; Wilfried Thiel; Matthias Rischer; Alfred Olbrich; and Bernhard Kutscher |
| Patent No.: | 6,538,151 |
| Issue Date: | March 25, 2003 |
| Expiration Date: | January 6, 2019 |

***(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings."***

A copy of U.S. Patent No. 6,538,151 ("the '151 patent"), for which this extension is sought, is attached hereto as Exhibit A.

***(8 ) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent."***

No terminal disclaimer was filed during the prosecution of the '151 patent.

No certificate of correction for the '151 patent was issued.

No reexamination certificate for the '151 patent was issued.

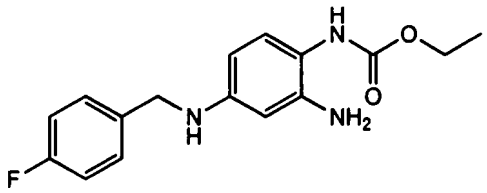
A copy of the receipts for 4th and 8th year maintenance fees payment is attached hereto as Exhibit E; thus, no maintenance fee is currently due. The 12th year maintenance fee is not due until 2014.

***(9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product;***
***(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and***
***(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product."***

The '151 patent claims, *inter alia*, the active ingredient of the approved product POTIGA™ and pharmaceuticals comprising the active ingredient. More specifically, at least independent claims 1 and 4 of the '151 patent claim the active ingredient of the approved product and pharmaceuticals comprising the ingredient. These claims are set forth below:

Claim 1

Modification A of the compound I




characterized by the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at 6.97°2θ (12.67 Å), 18.02°2θ (4.92 Å) and 19.94°2θ (4.45 Å).

Claim 4

Pharmaceuticals comprising the modification A, B or C of the compound I and, if appropriate, exipients [*sic*, excipients] and/or auxiliaries.

The approved product POTIGA™ contains ezogabine as the active ingredient comprising of form A. (*See* an excerpt from Drug Substance Development Report, Section 3.2.S.2.6, submitted to the FDA in connection with NDA, a copy of which is attached hereto as Exhibit F). Consequently, claims 1 and 4 of the '151 patent claim the approved product.

***(10) "A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:***

***(i) For a patent claiming a human drug, antibiotic, or human biological product:***

***(A) The effective date of the investigational new drug (IND) application and the IND number;***

***(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and***

***(C) The date on which the NDA was approved or the Product License issued."***

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for POTIGA™ are as follows:

(a) Investigational new drug ("IND") application number 53,950 was received by the FDA on August 15, 1997 and became effective on September 12, 1997.[2]

(b) The new drug application ("NDA") was submitted on October 30, 2009, and was later assigned NDA number 22-345.

(c) NDA number 22-345 was approved by the FDA on June 10, 2011 (Exhibit D).

[2] Although 30 days after the receipt of IND by FDA falls on September 14, 1997, FDA communicated no objection to proceed in a telephone conference that took place on September 12, 1997.

***(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities."***

A chronology of selected regulatory activities is attached hereto as Exhibit G to briefly describe certain activities undertaken with respect to the approval of POTIGA™ during the applicable regulatory review period and the dates applicable to such activities.

***(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined."***

Applicant is of the opinion that the '151 patent is eligible for an extension and estimates the extension to be **1794 days**, the calculation of which is described below.

A. Eligibility:

(a) Pursuant to 35 U.S.C. § 156(a), the '151 patent claims a product;

(b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '151 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '151 patent has never been extended under 35 U.S.C. §(e)(1);

(d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owner of record of the '151 patent or its agent;

(e) Pursuant to 35 U.S.C. § 156(a)(4), the approved product, POTIGA™, has been subject to a regulatory review period before its commercial marketing or use;

(f) Pursuant to 35 U.S.C. § 156(a)(5)(A), the permission for the commercial marketing or use of POTIGA™ after the regulatory review period is the first permitted commercial marketing or use of this product;

(g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for the approved product POTIGA™.

B. Regulatory Review Period:

(a) Pursuant to 37 C.F.R. § 1.775(c)(1), the period from September 12, 1997 (the date IND application number 53,950 became effective) to October 30, 2009 (the date the NDA was initially submitted) is 4431 days. Accordingly, Applicant calculates the "Testing Phase" as 4431 days.

(b) Pursuant to 37 C.F.R. § 1.775(c)(2), the period from October 30, 2009 (the

date the NDA was initially submitted) to June 10, 2011 (the date of NDA approval) is 588 days. Accordingly, Applicant calculates the "Approval Phase" as 588 days.

C. Extended Patent Term:

(a) The number of days in the regulatory review period which were on and before March 25, 2003, the date on which the '151 patent issued, is 2020 days. Accordingly, 2020 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.775(d)(1)(i). Thus, Applicant calculates the "Adjusted Testing Phase" to be 2411 days.

(b) As demonstrated in Exhibit F, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(ii).

(c) One half of the number of days remaining in the Testing Phase after the above reductions is 1206 days. Accordingly, 1205 days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(iii).

(d) The period remaining in the term of the patent (set to expire January 6, 2019) measured from the date of approval of POTIGA™ (June 10, 2011) (2,666 days) when added to the period of extension (1794 days) is 4,460 days, which is less than fourteen (14) years. Accordingly, the fourteen (14) year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) does not operate to further reduce the regulatory review period.

(e) The period of extension (1794 days) is less than five (5) years. Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.775(d)(5)(i)-(ii) does not operate to further reduce the regulatory review period.

Period of Extension = ½ (Adjusted Testing Phase) + Approval Phase
= ½ (2411) + 588
= **1794 days**

***(13) "A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought."***

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. § 1.765.

***(14) "The prescribed fee for receiving and acting upon the application for extension."***

The prescribed fee for receiving and acting upon this application is believed to be $1,120.00 pursuant to 37 C.F.R. § 1.20(j)(1). The Director is authorized to charge this fee and any additional required fees, or credit any overpayment, to Jones Day Deposit Account No. 50-3013.

***(15)(a) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed."***

Please direct all inquiries and correspondence relating to this application to:

David A. Gay
**JONES DAY**
222 East 41st Street
New York, New York 10017
(212) 326-3939

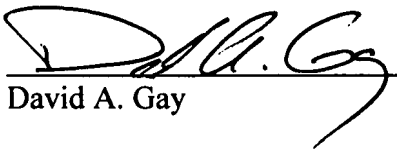
A power of attorney is also enclosed so that the record will reflect correspondence should be addressed to Customer No. 20583.

***(15)(b) "The application under this section must be accompanied by two additional copies of such application (for a total of three copies)."***

This Application is accompanied by two additional copies of such application for a total of three copies as required by 37 C.F.R. § 1.740(b). The undersigned attorney for Applicants hereby states that these copies are accurate and true duplicates of the original.

Respectfully submitted,

Date: August 8, 2011



39,200
David A. Gay (Reg. No.)

**JONES DAY**
222 East 41st Street
New York, NY 10017
(212) 326-3939

US006538151B1

Exhibit A

(12) **United States Patent**
**Meisel et al.**

(10) **Patent No.: US 6,538,151 B1**
(45) **Date of Patent: Mar. 25, 2003**

(54) **MODIFICATIONS OF 2-AMINO-4-(4-FLUOROBENZYLAMINO)-1-ETHOXYCARBONYLAMINOBENZENE, AND PROCESSES FOR THEIR PREPARATION**

(75) Inventors: **Peter Meisel**, Dresden (DE); **Karl-Friedrich Landgraf**, Dresden (DE); **Jürgen Schäfer**, Radebeul (DE); **Wilfried Thiel**, Langebüuch (DE); **Matthias Rischer**, Maintal (DE); **Alfred Olbrich**, Halle/Westf. (DE); **Bernhard Kutscher**, Maintal (DE)

(73) Assignee: **Asta Medica Aktiengesellschaft**, Dresden (DE)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 362 days.

(21) Appl. No.: **09/181,671**

(22) Filed: **Oct. 29, 1998**

**Related U.S. Application Data**

(63) Continuation of application No. 09/004,926, filed on Jan. 9, 1998, now Pat. No. 5,914,425.

(30) **Foreign Application Priority Data**

Jan. 20, 1997 (DE) ..... 197 01 694

(51) **Int. Cl.**[7] ..... **C07C 269/08**; C07C 271/28
(52) **U.S. Cl.** ..... **560/27**
(58) **Field of Search** ..... 560/27

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,384,330 A 1/1995 Dieter et al.

OTHER PUBLICATIONS

Kirk–Othmer Encyclopedia of Chemical Technology, 3rd ed., vol. 7, John Wiley and Sons, Inc., 1979, pp. 251–255.*
Kirk–Othmer Encyclopedia of Chemical Technology, 4th ed., vol. 7, John Wiley and Sons, Inc., 1993, pp. 700–702.*

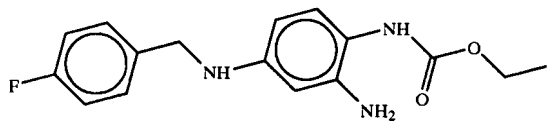
* cited by examiner

*Primary Examiner*—Brian Davis
(74) *Attorney, Agent, or Firm*—Venable; Ann S. Hobbs

(57) **ABSTRACT**

The invention relates to novel modifications of the compound 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene of the

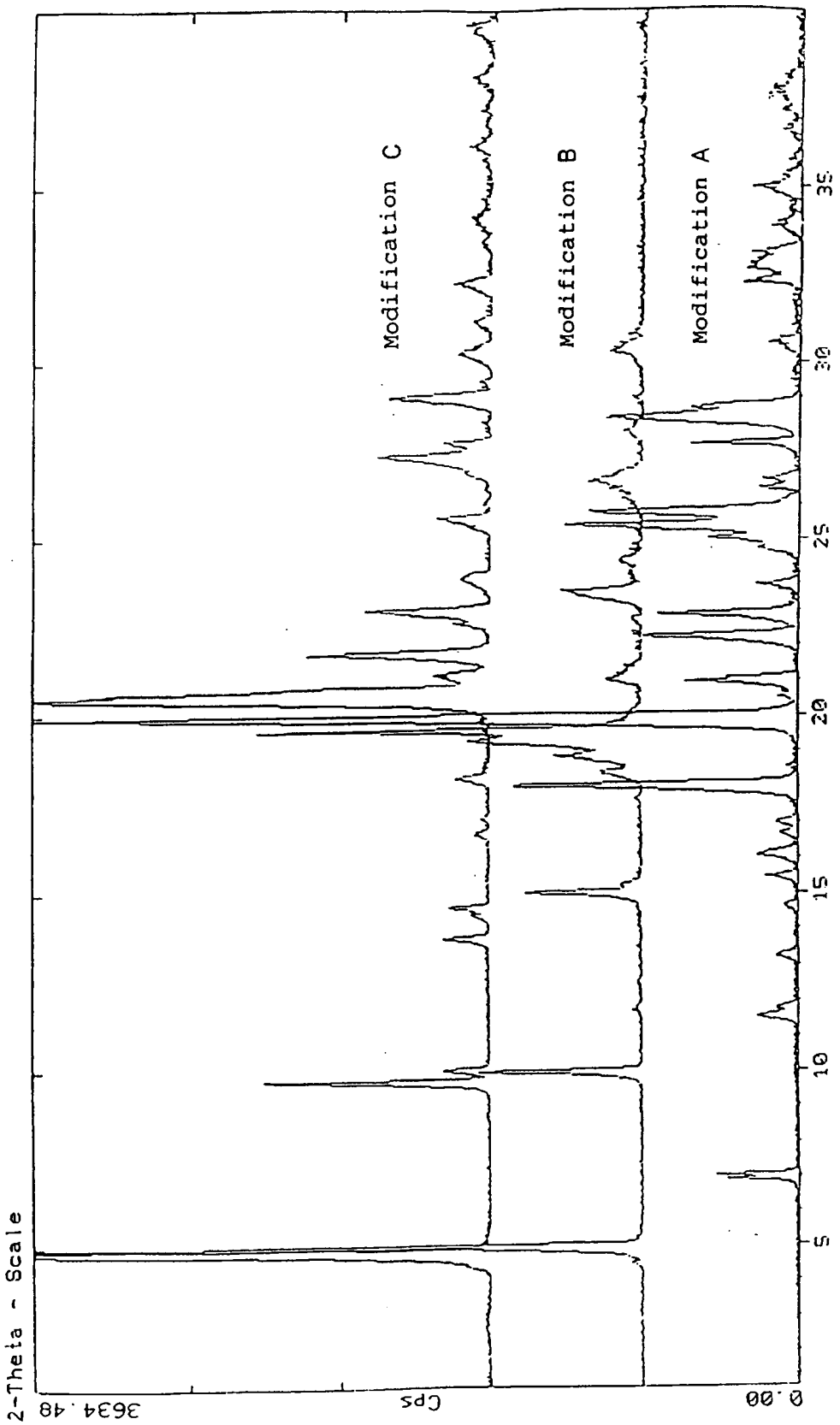
formula I




processes for their preparation and their use in pharmaceutical compositions.

**4 Claims, 5 Drawing Sheets**

Figure 1


Modification C
Modification B
Modification A
2-Theta - Scale
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Cps
0.00
5
10
15
20
25
30
35

Figure 2

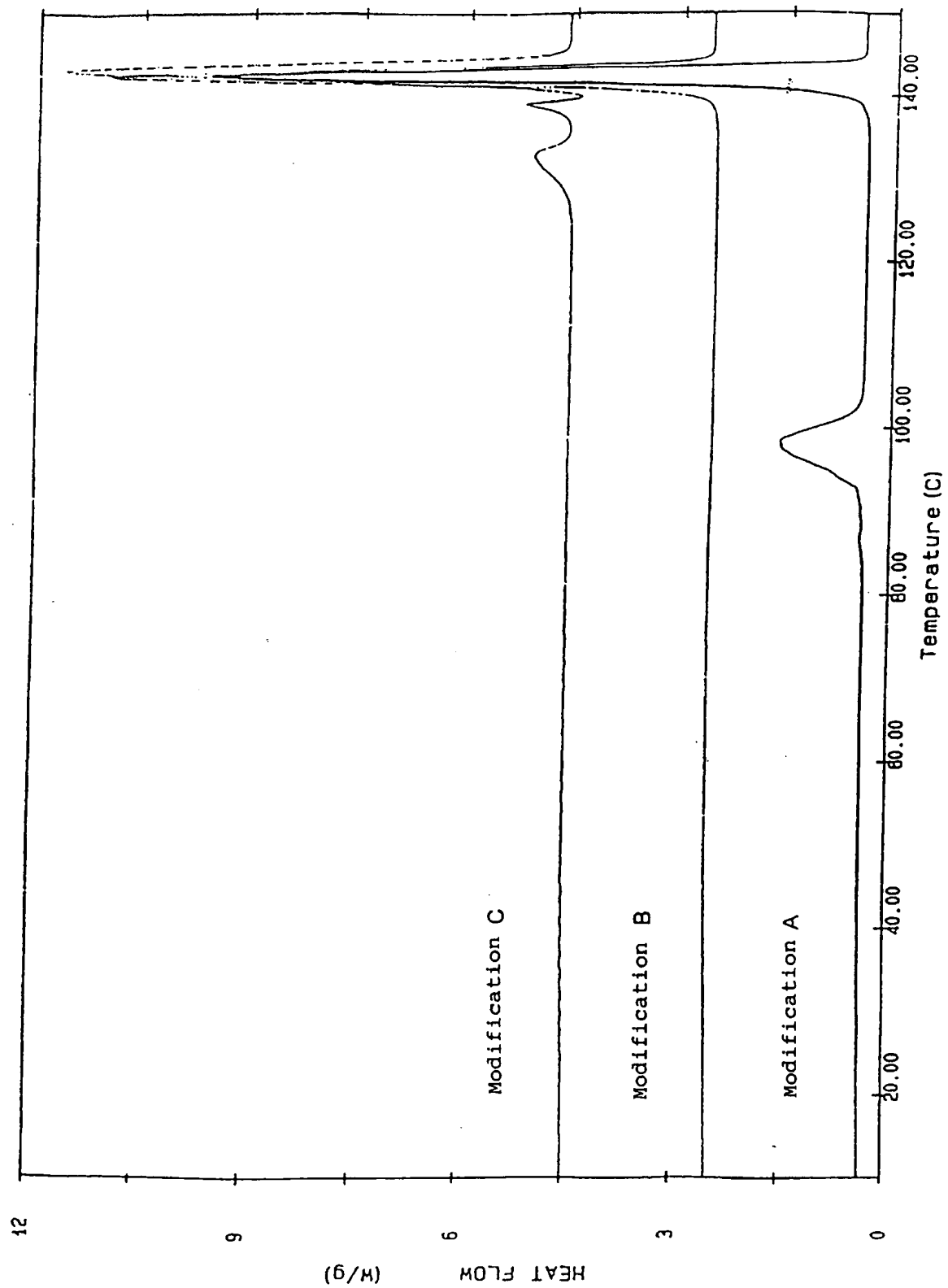
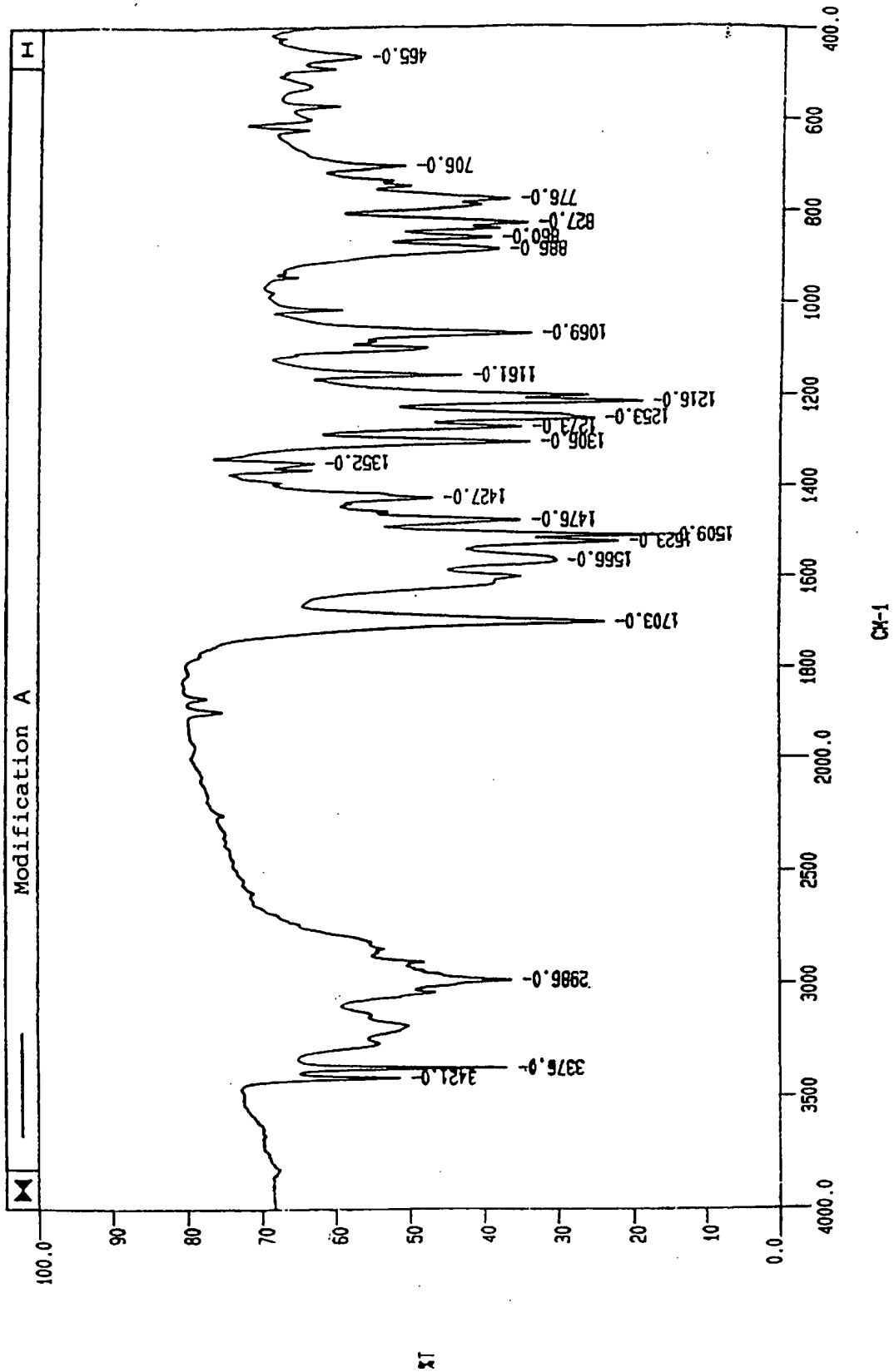

Modification C
Modification B
Modification A
HEAT FLOW (W/g)
12
9
6
3
0
20.00
40.00
60.00
80.00
100.00
120.00
140.00
Temperature (C)

Figure 3a


Modification A
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706.0
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860.0
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1069.0
1161.0
1216.0
1253.0
1273.0
1306.0
1352.0
1427.0
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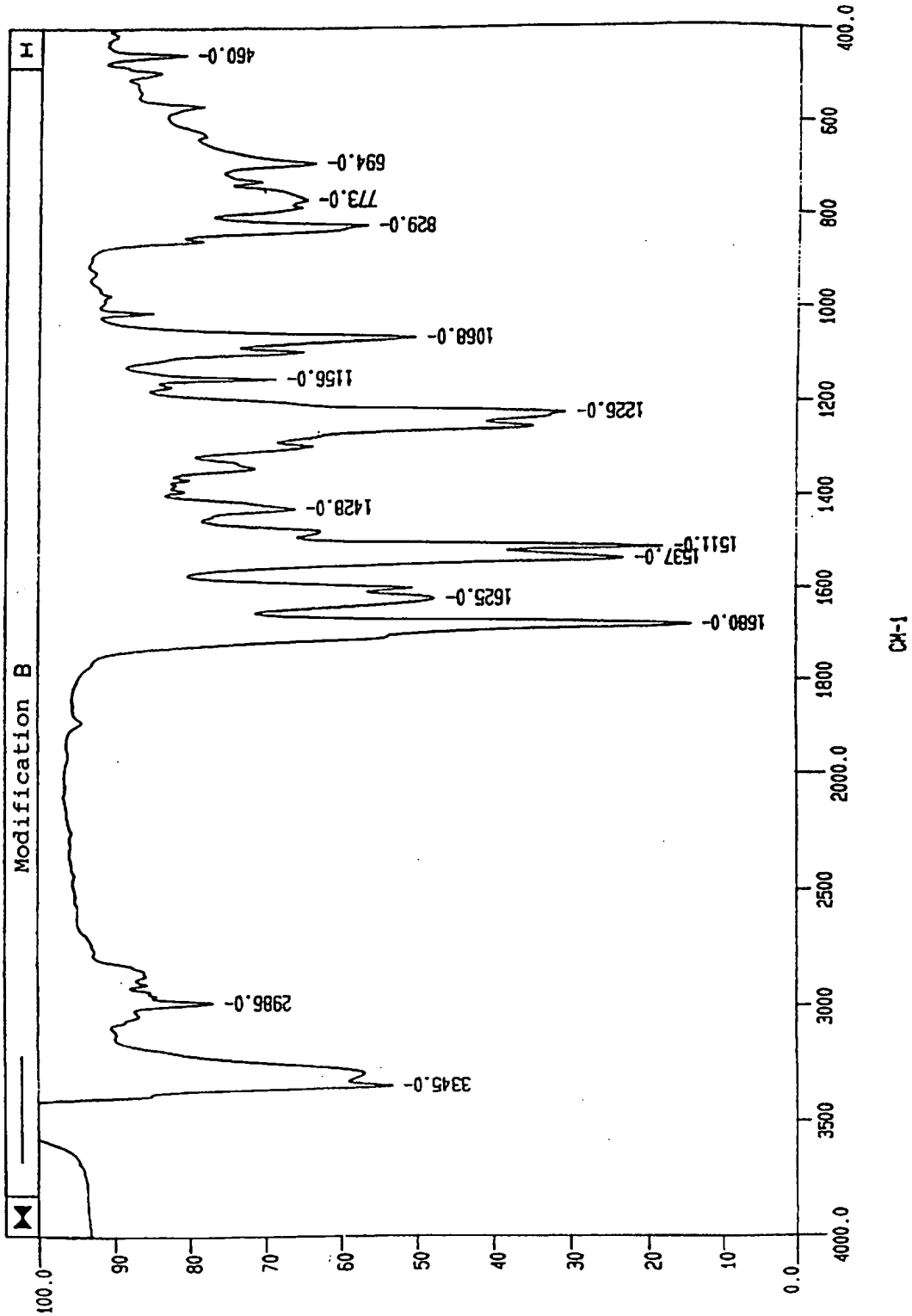
3376.0
3421.0
CM-1

Figure 3b


Modification B
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1156.0
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1428.0
1511.0
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1625.0
1680.0
2986.0
3345.0
4000.0
3500
3000
2500
2000.0
1800
1600
1400
1200
1000
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600
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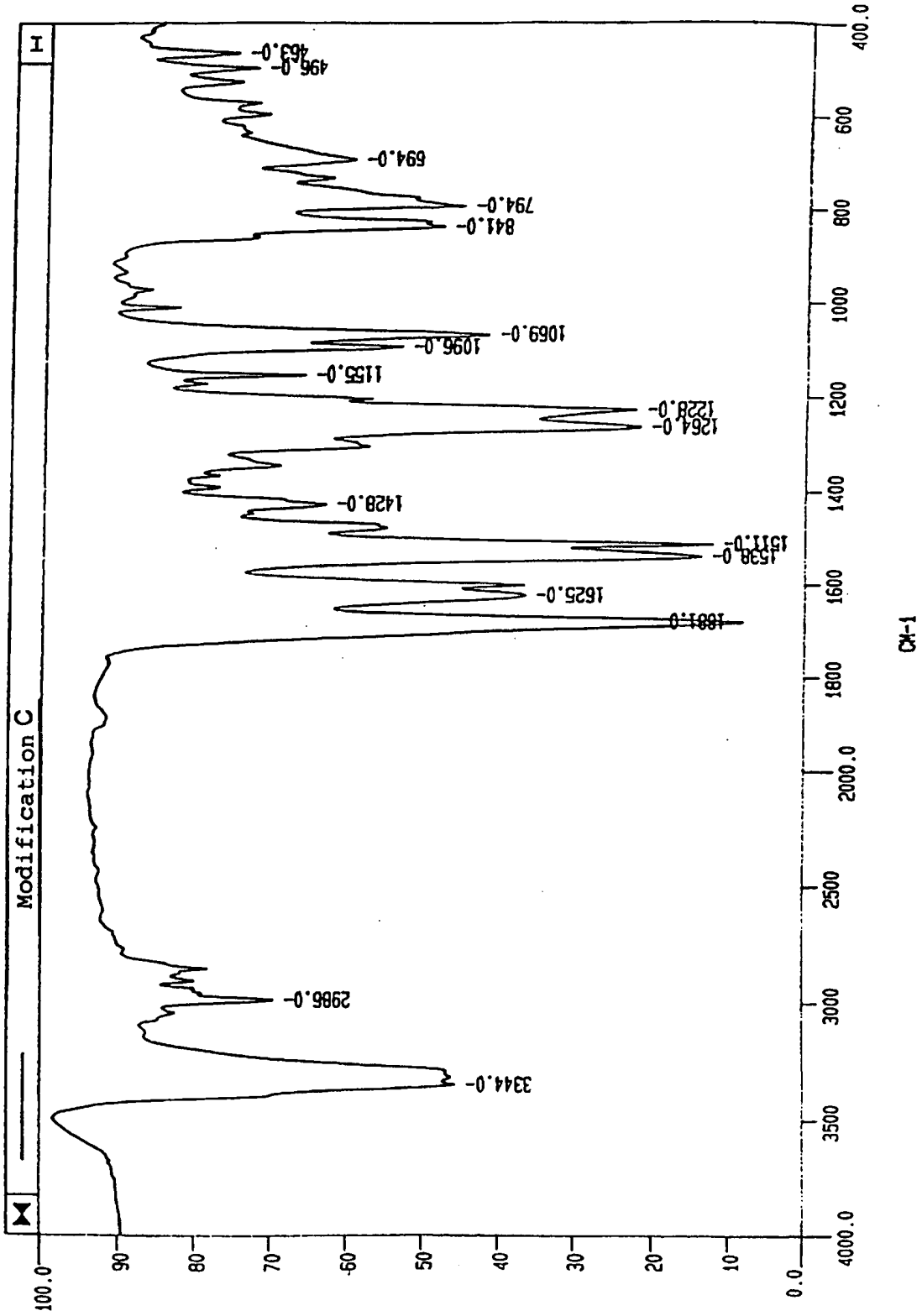
80
70
60
50
40
30
20
10
0.0
CM-1

Figure 3c


Modification C
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694.0
794.0
841.0
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1264.0
1428.0
1511.0
1538.0
1625.0
1881.0
2986.0
3344.0
100.0
90
80
70
60
50
40
30
20
10
0.0
4000.0
3500
3000
2500
2000.0
1800
1600
1400
1200
1000
800
600
400.0
CM-1

# MODIFICATIONS OF 2-AMINO-4-(4-FLUOROBENZYLAMINO)-1-ETHOXYCARBONYLAMINOBENZENE, AND PROCESSES FOR THEIR PREPARATION

This is a continuation of application Ser. No. 09/004,926, filed Jan. 9, 1998 now U.S. Pat. No. 5,914,425.

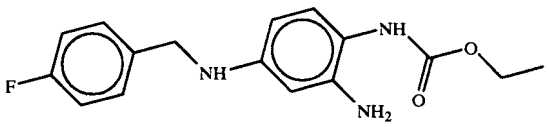
## BACKGROUND OF THE INVENTION

1. Field of the Invention

Novel modifications of 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene, and processes for their preparation

The invention relates to novel modifications of the compound 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene of the

formula I




processes for their preparation and their use in pharmaceutical compositions.

2. Background Information

The compound of the formula I and its preparation is described in the patent DE 42 00 259.

This compound has, for example, anticonvulsive, antipyretic and analgesic activity and can thus be employed in pharmaceutical preparations.

In the crystallization of the compound of the formula I, however, in some cases very different mixed products are obtained with respect to the crystal size and form. Mixtures of crystal modifications are a great problem for pharmaceutical preparations. In particular, in the case of pharmaceutical forms having a high active compound content, physical inhomogeneties have a disadvantageous effect on adherence to constant pharmaceutical production conditions.

On the other hand, considerable variations in the stability, purity and uniformity of the finished product occur, so that the demands on the pharmaceutical quality of an active compound cannot be satisfied.

It is therefore of great interest to prepare the compound of the formula I in homogeneous crystalline form.

## SUMMARY OF THE INVENTION

The invention is thus based on the object of preparing the compound of the formula I in homogeneous crystalline form which meets the pharmaceutical requirements.

It has now surprisingly been found that the compound of the formula I can be prepared in 3 different pure crystal modifications. Thus physically homogeneous compounds of the formula I can be prepared for the production of pharmaceutical finished products.

The 3 modifications, called A, B and C, have different physicochemical properties.

The in each case characteristic X-ray diffractograms are used for the identification of these three modifications of the compound of the formula I.

The modifications furthermore differ in their DSC curves (differential scanning calorimetry) and in some cases also in their IR spectra as well as by the crystal forms typical in each case.



## BRIEF DESCRIPTION OF THE DRAWINGS

The X-ray diffractograms according to FIG. **1** were recorded with a powder diffractometer using $CuK_\alpha$ radiation.

The data for the DSC curve according to FIG. **2** relate to a heating rate of 10 k/min. The temperatures given in each case indicate the position of the intensity maximum.

The IR spectra illustrated (FIGS. *3a, b, c*) were recorded on KBr pressed discs.

## DETAILED DESCRIPTION OF THE INVENTION

The modification A is characterized by

the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at 6.97°2θ (12.67 Å), 18.02°2θ (4.92 Å) and 19.94°2θ (4.45 Å),

the endothermic A, B conversion effect at approx. 97° C. (maximum) below the melting effect of the modification b at approx. 142° C. in the DSC curve,

the IR spectrum differing from the other two modifications by intensive vibration bands at 3421 $cm^{-1}$ (ν N—H) 3376 $cm^{-1}$ (ν N—H), 1703 $cm^{-1}$ (ν C=O) and 886 $cm^{-1}$ (γ C—H), and

mainly nearly isometric to short-columnar crystals.

The modification B is characterized by

the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at 15.00°2θ (5.90 Å), 19.29°2θ (4.60 Å) and 19.58°2θ (4.53 Å),

the absence of thermal effects below the melting effect at approx. 142° C. in the DSC curve and

mainly longish-tabular to columnar crystals.

The modification C is characterized by

the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at 9.70°2θ (9.11 Å) and 21.74°θ (4.09 Å),

two endothermic effects connected with the phase transmission to the modification B between approx. 130° C. and the melting effect of the modification B at approx. 142° C. in the DSC curve and

mainly tabular crystals.

The preparation of the 3 modifications of the compound I can be carried out by the following processes, adherence to the conditions being of particular importance.

The modifications can be prepared either from the crude product of the compound of the formula I or alternatively by modification conversion.

### Preparation of the Modification A

The modification A can be prepared from the modifications B and C by stirring in solvents.

The crystallization of the modification A is preferably carried out with stirring of a supersaturated solution of the compound I in protic, dipolar-aprotic or non-polar solvents.

Protic solvents which can be employed are lower alcohols such as ethanol, 2-propanol, n-butanol, dipolar-aprotic solvents are acetonitrile or acetone and non-polar solvent is toluene.

The crystallization is preferably carried out in the presence of lower alcohols. The crystallization from the solution is carried in the temperature range from −20° C. to 110° C.

In particular, in certain solvents, such as n-butanol, the crystallization of the pure modification A can be carried out at temperatures up to 110° C. The pure modification A is preferably obtained by crystallization in the temperature range from 20° C. to 50° C.

Preparation of the Modification B

The crystallization of the modification B is carried out from a saturated solution of the compound I with slow cooling.

The solvents employed can be protic solvents such as water or aprotic solvents such as toluene.

The crystallization is preferably carried out in the presence of toluene.

The crystallization from the solution can be carried out in the temperature range between 50° C. and 110° C., but preferably between 80° C.–100° C.

The modification B can also be obtained by thermal phase conversion, preferably from the modification A at temperatures of greater than 80° C.

Preparation of the Modification C

The modification C crystallizes out at a temperature of 30° C.–80° C. with slow cooling from a saturated solution of the compound I in protic solvents such as ethanol and 2-propanol or aprotic solvents such as toluene.

The crystallization from the solution is preferably carried out at a temperature of 50° C.–70° C.

Each of these modifications of the compound I can be processed for administration in pharmaceutical forms which satisfy the pharmaceutical demands.

The present invention further relates to the use of the modifications A, B and C of the compound I for the production of pharmaceutical preparations. In particular, they are efficacious anti-epileptic agents and neuroprotective agents.

The pharmaceutical preparations can in general contain between 10 mg and 200 mg of at least one of the modifications of the compound I as an individual dose. Preferred administration forms are tablets.

The modifications of the compound of the formula I can be processed to give the pharmaceutical preparation in a customary manner using suitable exipients and/or auxiliaries.

The modification A of the compound I in particular shows advantageous properties for further pharmaceutical processing.

- The crystal structure is stable up to approx. 80° C. Even after relatively long storage at temperatures up to 60° C. and relative atmospheric humidities up to 70%, no lattice changes are observed.
- The modification A undergoes no lattice change on contact with solvents such as, for example, water, ethanol, acetone or toluene.
- The nearly isometric to short-columnar crystal form leads to a grainy substance structure convenient for pharmaceutical processing.

The modifications B and C can be employed for specific pharmaceutical forms such as capsules and dry ampoules. Thus, for example, the preferred formation of finely granular and therefore particularly rapidly soluble crystals observed with the modification C can have advantages for the production of dry ampoules.

The preparation processes for the individual modifications will be illustrated in greater detail with the aid of examples:

EXAMPLE 1

Modification A

2.34 kg of the compound I and 0.16 kg of active carbon are dissolved by warming with stirring in 7.0 l of ethanol in a 16-1 dissolving vessel. The solution is filtered hot through a pressure filter with stirring into a cooled 32-1 crystallizing vessel with 0.5 l of ethanol such that the internal temperature in the crystallizing vessel is kept at <45° C. The remaining solution is then rinsed from the dissolving vessel through the pressure filter into the crystallizing vessel using 0.75 l of hot ethanol and the suspension is swiftly cooled. It is subsequently stirred at 5° C.–12° C. for 0.5 hours and the solid is filtered off with suction under inert conditions. The product is washed three times with 1.2 l of cooled ethanol each time. The crystallizate is then dried to weight constancy at 50° C.–55° C. in a vacuum drying oven. 2.04 kg (87% of theory) of the pure modification A is obtained.

EXAMPLE 2

Modification A

2 g of the modification C are stirred for 2 days at room temperature in 6 ml of ethanol. The modification A is obtained quantitatively.

EXAMPLE 3

Modification A

5 g of the modification B or C are stirred for 2 days at room temperature in 50 ml of toluene. The modification A is obtained quantitatively.

EXAMPLE 4

Modification A

3 g of the modification B are stirred for 2 days at room temperature in 1.5 ml of acetone. The modification A is obtained quantitatively.

EXAMPLE 5

Modification A

10 g of the compound I are dissolved in 5 ml of n-butanol with warming. The solution is allowed to crystallize at 105° C.–110° C., the mixture is cooled to 20° C. and the crystals are washed with n-butanol after filtering off with suction. The modification A is obtained quantitatively.

EXAMPLE 6

Modification B

10 g of the compound I are briefly heated to reflux with 20 ml of toluene and dissolved. The solution is allowed to crystallize at 90° C.–100° C. and the crystals are filtered off with suction and washed with 5 ml of toluene. After drying, 9.8 g (98% of theory) of needle-shaped crystals are obtained.

EXAMPLE 7

Modification B

10 g of substance of the modification A are kept for 8 hours at 100° C. in a drying oven. The modification B is obtained quantitatively.

EXAMPLE 8

Modification C

3.0 kg of the compound I are dissolved in a 32-1 dissolving vessel by stirring with warming after addition of 0.2 kg

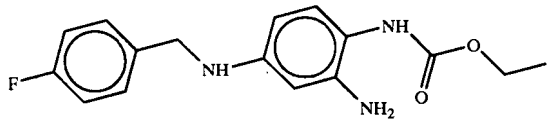
of active carbon in 19.6 l of isopropanol. The solution is filtered hot through a pressure filter into a 32-1 crystallizing vessel such that the internal temperature in the crystallizing vessel is kept at 60–65° C. The remaining solution is then rinsed from the dissolving vessel through the pressure filter into the crystallizing vessel using 2.5 l of hot isopropanol (about 70° C.). After the start of crystallization at 60° C.–65° C., the mixture is subsequently stirred. The suspension formed is swiftly cooled, subsequently stirred at 5° C.–12° C. and filtered off with suction under inert conditions. The crystallizate is washed three times with 2.5 l of cooled isopropanol each time.

The crystallizate is then dried to weight constancy in vacuo at 50° C.–55° C. 2.64 kg (88% of theory) of the active compound are obtained in modification C.

What is claimed is:

1. Modification A of the compound I

formula I




characterized by the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at 6.97°2θ (12.67 Å), 18.02°2θ (4.92 Å) and 19.94°2θ (4.45 Å).

2. Modification B of the compound I characterized by the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at 15.00°2θ (5.90 Å), 19.29°2θ (4.60 Å) and 19.58°2θ (4.53 Å).

3. Modification C of the compound I characterized by the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at 9.70°2θ (9.11 Å) and 21.74°θ (4.09 Å).

4. Pharmaceuticals comprising the modification A, B or C of the compound I and, if appropriate, exipients and/or auxiliaries.

* * * * *

Exhibit 3

**UNITED STATES DEPARTMENT OF COMMERCE**
**Patent and Trademark Office**
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FEBRUARY 25, 1999

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PILLSBURY MADISON & SUTRO LLP
ANN S. HOBBS
1100 NEW YORK AVENUE, N.W.
NINTH FLOOR, EAST TOWER
WASHINGTON, D.C. 20005-3918

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RECORDATION DATE: 10/29/1998

REEL/FRAME: 9562/0753
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

| | |
|---|---|
| ASSIGNOR:<br>MEISEL, PETER | DOC DATE: 02/17/1998 |
| ASSIGNOR:<br>LANDGRAF, KARL-FRIEDRICH | DOC DATE: 02/18/1998 |
| ASSIGNOR:<br>SCHAFER, JURGEN | DOC DATE: 02/25/1998 |
| ASSIGNOR:<br>THIEL, WILFRIED | DOC DATE: 02/18/1998 |
| ASSIGNOR:<br>RISCHER, MATTHIAS | DOC DATE: 03/02/1998 |
| ASSIGNOR:<br>OLBRICH, ALFRED | DOC DATE: 03/06/1998 |
| ASSIGNOR:<br>KUTSCHER, BERNHARD | DOC DATE: 02/27/1998 |

ASSIGNEE:
ASTA MEDICA AKTIENGESELLSCHAFT
AN DER PIKARDIE 10
D-01277 DRESDEN, FED REP GERMANY

SERIAL NUMBER: 09181671
PATENT NUMBER:

FILING DATE: 10/29/1998
ISSUE DATE:

ALLYSON PURNELL, EXAMINER
ASSIGNMENT DIVISION
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BOX ASSIGNMENTS

11-09-1998

100876999

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SIR: PLEASE RECORD THE ATTA

THEREOF.

1. NAME OF CONVEYING PARTY(IES) (ASSIGNORS(S)):
1. MEISEL, Peter
2. LANDGRAF, Karl-Friedrich
3. SCHAFER, Jurgen
4. THIEL, Wilfried
5. RISCHER, Matthias
6. OLBRICH, Alfred
7. KUTSCHER, Bernhard
8.

MRD

ADDITIONAL NAME(S) OF CONVEYING PARTY(IES) ATTACHED? ☐YES ☒NO 10-29-98

U.S. PTO
09/181671
10/29/98

2. PARTY(IES) (ASSIGNEE(S)) RECEIVING INTEREST:

NAME: ASTA Medica Aktiengesellschaft

ADDRESS: An der Pikardie 10, D-01277 Dresden, GERMANY

ADDITIONAL NAME(S) & ADDRESS(ES) ATTACHED? ☐YES ☒NO

3. NATURE OF CONVEYANCE (DOCUMENT):
(Submit herewith only one document for recordation—multiple copies of same Assignment signed by different inventors is one document)

☒ASSIGNMENT OF ☒WHOLE ☐PART INTEREST

**EXEC. DATE:** 1. 17 Feb 1998; 2. 18 Feb 1998; 3. 25 Feb 1998; 4. 18 Feb 1998; 5. 2 Mar 1998; 6. 6 Mar 1998; and 7. 27 Feb 1998

☐CHANGE OF NAME ☐VERIFIED TRANSLATION
☐SECURITY ☐MERGER ☐**OTHER:**

EXECUTION DATE(S) ON THE DECLARATION IF FILED HEREWITH: (**NOTE**: IF DATES ON DECLARATION AND ASSIGNMENT DIFFER SEE ATTY!) Same as above

4.5 APPL. NO.(S) OR PAT NO.(S). OTHERS ON ADDITIONAL SHEET(S) attached? ☐YES ☒NO

| A. PAT. APP. NO.(S) series code/serial no | M# | 1st INVENTOR if not in item 1 | B. PATENT NO(S) | M# | 1st INVENTOR if not in item 1 |
|---|---|---|---|---|---|
| 09/181,671 | 256868 | | | | |

5. Name & Address of Party to Whom Correspondence Concerning Document Should be Mailed:
**Pillsbury Madison & Sutro LLP**
**Intellectual Property Group**
1100 NEW YORK AVENUE, N.W.
NINTH FLOOR, EAST TOWER
WASHINGTON, D.C. 20005-3918

6. NUMBER INVOLVED:
APPLNS 1 + PATS: 0 = TOTAL 1

7. AMOUNT OF FEE ENCLOSED: (Code 581)
ABOVE TOTAL x $40 = $40

5.5 ATTY DKT:

| PMS 256868 | 97/01PH/EN |
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| MATTER NO. | CLIENT REF. |

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| dup. sheet not required | CLIENT NO. | MATTER NO. |

9. STATEMENT AND SIGNATURE.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

04/1998 GDUCKETT 00000009 09181671
FC:581 1 40.00 OP

Signature

Attorney: Ann S. Hobbs
Reg. No. 36830
Atty/Sec: ASH/kim

| 10. Total number of pages including this cover sheet, attachments and document (do not file dup. Cover sheet) | 3 |
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Date: October 29, 1998
TEL: (202) 861-3063
FAX: (202) 822-0944

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# ASSIGNMENT
(Continued from page 1)

LISTING OF ADDITIONAL INVENTORS

INSERT NAME(S) OF INVENTOR(S)

| | |
|---|---|
| (6) Alfred OLBRICH | (11) |
| (7) Bernhard KUTSCHER | (12) |
| (8) | (13) |
| (9) | (14) |
| (10) | (15) |

## SIGNATURES OF ADDITIONAL INVENTORS/WITNESSES/DATES SIGNED

| | INVENTOR(S) | DATE SIGNED | WITNESSES |
|---|---|---|---|
| 6) Name: Alfred OLBRICH | A. Olbrich | 6.3.98 | Eva-M. Ludwig |
| 7) Name: Bernhard KUTSCHER | B. Kutscher | 27.2.98 | A. Schmid |
| 8) Name: | | | |
| 9) Name: | | | |
| 10) Name: | | | |
| 11) Name: | | | |
| 12) Name: | | | |
| 13) Name: | | | |
| 14) Name: | | | |
| 15) Name: | | | |

Please return signed/recorded to:
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Intellectual Property Group of
Pillsbury Madison & Sutro LLP
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1100 New York Avenue, N.W.
Washington, D.C. 20005-3918

USA Patent Appln.
Sole or Joint

For Inventions made outside USA executed with or after application

| Atty. Dkt. | 244517 | 97/01 PH/EN |
|---|---|---|
| | M# | Client Ref. |

NONPROVISIONAL

# ASSIGNMENT OF NONPROVISIONAL APPLICATION

NONPROVISIONAL

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, undersigned, to wit:

INSERT NAME(S) OF INVENTOR(S)

| | |
|---|---|
| (1) Peter MEISEL | (4) Wilfried THIEL |
| (2) Karl-Friedeich LANDGRAF | (5) Matthias RISCHER |
| (3) Jürgen SCHÄFER | [X] x box if continued on page 2 |

who at the request of, hereby sell(s), assign(s) and transfer(s) unto:

INSERT NAME(S) OF ASSIGNEE(S) & ADDRESS(ES)

ASTA Medica Aktiengesellschaft
An der Pikardie 10
D-01277 Dresden
GERMANY

(hereinafter designated "ASSIGNEE") the entire right, title and interest for the United States of America as defined in 35 U.S.C. 100, in the invention and all applications including any and all divisions, continuations, substitutes, and reissues thereof, and all resulting patents, known as

TITLE OF INVENTION: NOVEL MODIFICATIONS OF 2-AMINO-4-(4-FLUOROBENZYLAMINO)-1-ETHOXYCARBONYLAMINOBENZENE, AND PROCESSES FOR THEIR PREPARATION

for which the undersigned executed an application for Letters Patent of the United States of America:

NOTE →→ (Complete line A, B and/or C)

(A) [ ] even date herewith
(B) [ ] on _____
(C) [X] in U.S. Appln. No. / filed January 9, 1998

AND the undersigned hereby authorize(s) and request(s) the United States Commissioner of Patents and Trademarks to issue said Letters Patent to the said ASSIGNEE, for its interest as ASSIGNEE, its successors, assigns and legals representatives; the undersigned agree(s) that the attorney of record in said application shall hereinafter act on behalf of said ASSIGNEE;

AND the undersigned hereby agree(s) to testify and execute any papers for ASSIGNEE, its successors, assigns and legal representatives, deemed essential by ASSIGNEE to ASSIGNEE'S full protection and title in and to the invention hereby transferred.

NOTE →→ The undersigned hereby authorize(s) Cushman Darby & Cushman Intellectual Property Group of Pillsbury Madison & Sutro, of the above address to insert hereon any further identification necessary or desirable for recordation of this document.

| | INVENTOR(S) | DATE SIGNED | WITNESSES |
|---|---|---|---|
| 1) | P. Meisel | 17.2.98 | Petra Gudd |
| Name: | Peter MEISEL | | |
| 2) | K. Landgraf | 18.2.98 | H. Hoffmann |
| Name: | Karl-Friedrich LANDGRAF | | |
| 3) | J. Schäfer | 25.02.98 | Jäm |
| Name: | Jürgen SCHÄFER | | |
| 4) | W. Thiel | 18.2.98 | Hoffmann |
| Name: | Wilfried THIEL | | |
| 5) | M. Risch | 2.3.98 | MRR |
| Name: | Matthias RISCHER | | |

IF ADDITIONAL INVENTORS, check box [X] and continue on page 2.

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**CORRECTED NOTICE**
ASH
39375-175024

MAY 12, 2003

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P.O. BOX 34385
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39375-176486
39375-174586
39375-174646

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RECORDATION DATE: 10/21/2002

REEL/FRAME: 013411/0778
NUMBER OF PAGES: 10

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ASTA MEDICA AG

DOC DATE: 11/05/2001

ASSIGNEE:
VIATRIS GMBH & CO. KG
WEISMULLERSTRASSE 45
FRANKFURT AM MAIN, FED REP
GERMANY
60314

SERIAL NUMBER: 07519172
PATENT NUMBER:

FILING DATE: 05/04/1990
ISSUE DATE:

SERIAL NUMBER: 08281973
PATENT NUMBER:

FILING DATE: 07/29/1994
ISSUE DATE:

SERIAL NUMBER: 07935656
PATENT NUMBER:

FILING DATE: 08/26/1992
ISSUE DATE:

SERIAL NUMBER: 09463300
PATENT NUMBER:

FILING DATE: 08/15/2000
ISSUE DATE:

| | |
|---|---|
| SERIAL NUMBER: 09784640<br>PATENT NUMBER: 6436924 | FILING DATE: 02/15/2001<br>ISSUE DATE: 08/20/2002 |
| SERIAL NUMBER: 09708703<br>PATENT NUMBER: 6545039 | FILING DATE: 11/09/2000<br>ISSUE DATE: 04/08/2003 |
| SERIAL NUMBER: 09247204<br>PATENT NUMBER: 6376550 | FILING DATE: 02/09/1999<br>ISSUE DATE: 04/23/2002 |
| SERIAL NUMBER: 60075332<br>PATENT NUMBER: | FILING DATE: 02/20/1998<br>ISSUE DATE: |
| SERIAL NUMBER: 09181671<br>PATENT NUMBER: 6538151 | FILING DATE: 10/29/1998<br>ISSUE DATE: 03/25/2003 |
| SERIAL NUMBER: 09349564<br>PATENT NUMBER: 6436438 | FILING DATE: 07/08/1999<br>ISSUE DATE: 08/20/2002 |
| SERIAL NUMBER: 08531978<br>PATENT NUMBER: | FILING DATE: 09/21/1995<br>ISSUE DATE: |
| SERIAL NUMBER: 08212578<br>PATENT NUMBER: | FILING DATE: 03/17/1994<br>ISSUE DATE: |

DOROTHY WILLIAMS, PARALEGAL
ASSIGNMENT DIVISION
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OMB No. 0651-0027 (exp. 5/31/2002)

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1. Name of conveying party(ies):

**ASTA MEDICA AG**

10/21/02

Additional name of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: **VIATRIS GmbH & Co. KG**

Internal Address:

Street Address: **Weismüllerstrasse 45**

City: **Frankfurt am Main** State/Country: **Germany**

Zip: **60314**

Additional Name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment ☐ Merger

☐ Security Agreement ☒ Change of Name

☐ Other

Execution Date: **November 5, 2001**

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application by the first named inventor is:

A. Patent Application No.(s)

**07/519,172**
**08/281,973**
**07/935,656**

B. Patent No.(s)

Additional numbers attached? ☒ Yes ☐ No – **SEE ATTACHED PAGE FOR ADDITIONAL APPLICATION NOS.**

5. Name and address of party to whom correspondence concerning this document should be mailed:

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VENABLE ATTORNEYS AT LAW PC Docs No. **409458v1**

**ADDITIONAL APPLICATION NOS.**

08/212,578

08/531,978

09/349,564

09/181,671

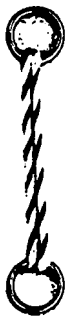
60/075,332

09/247,204

09/708,703

09/784,640

09/463,300



**Acknowledgement of Assignment**

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| U.S. Patent Application Nos.: | Filing dates: |
|---|---|
| 07/519172 | 4 May 1990 |
| 08/281,973 | 4 May 1990 |
| 07/935,656 | 26 August 1992 |
| 08/212,578 | 17 March 1994 |
| 08/531,978 | 21 September 1995 |
| 09/349,564 | 18 July 1997 |
| 09/181,671 | 9 January 1998 |
| 60/075,332 | 9 February 1999 |
| 09/247,204 | 9 February 1999 |
| 09/708,703 | 9 November 2000 |
| 09/784,640 | 15 February 2001 |
| 09/463,300 | 22 July 1998 |

I/we hereby authorize and request the United States Commissioner of Patents and Trademarks to issue any and all patents that may be granted on said Patent Applications; and to recognize VIATRIS GmbH & Co. KG and its legal representatives and assigns as having the entire right, title and interest in said Patent Applications and Patents, the same to be held and enjoyed by VIATRIS GmbH & Co. KG for its own use and behoof to the full end of the term for which any said Patent is granted.

ASTA MEDICA AG

Date November 5, 2001

By _____

Typed Name: Hans-Jürgen Krömp Norbert Leonhard

Title: Head of Legal Dep. Head of Tax Dep

**No. 3652 of the Roll of Deeds of 2002**

I hereby certify, that the above are the true signatures, respectively acknowledged in my presence of

1. Mr. Hans-Jürgen **Kromp,** born 15th of November 1953,

2. Mr. Norbert **Leonhard,** born 28th of December 1960,
both with business address at Weismüllerstraße 45,
60314 Frankfurt am Main,

- who are personally known to me -,

both acting on behalf of **ASTA Medica AG**, a juristic person duly organized under the laws of Germany and with registered office at Dresden and registered in the Commercial Register of the Dresden Local Court under No. HRB 7131.

At the same time I confirm that according to the certified excerpt of the Commercial Register of the Dresden Local Court dated December 21st, 2001, Mr. Kromp and Mr. Leonhard were procurists of ASTA Medica AG at Dresden and were entitled to represent this company jointly on November 5, 2001.

Upon request the aforementioned persons denied prior activities of the Notary in this matter as regulated by § 3 sec. 1 No. 7 BeurkG.

Frankfurt am Main, this 25th day of September 2002

Gregor Segner, Attorney of Law
officially appointed representative of Notary
Dr. Klaus D. Hartmann

**Statement of costs**

| | |
|---|---|
| Value of the matter: € 50.000,00 | |
| 5/20 fee §§ 141, 32, 45/1 KostO | € 33,00 |
| fee § 150 I KostO | € 13,00 |
| 16 % VAT § 151a KostO | € 7,36 |
| Total | € 53,36 |

Gregor Segner, Attorney of Law
as officially appointed representative of Notary
Dr. Klaus D. Hartmann

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

SEPTEMBER 30, 2004

PTAS

*102720507A*

PILLSBURY WINTHROP LLP
RICHARD BLAYBLOCK
INTELLECTUAL PROPERTY GROUP
11682 EL CAMINO REAL, SUITE 200
SAN DIEGO, CA 92130-2092

UNITED STATES PATENT AND TRADEMARK OFFICE
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RECORDATION DATE: 04/09/2004

REEL/FRAME: 015190/0936
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: 057602-0309221

ASSIGNOR:
VIATRIS GMBH & CO. KG

DOC DATE: 01/24/2004

ASSIGNEE:
XCEL PHARMACEUTICALS, INC.
6363 GREENWICH DRIVE, SUITE 100
SAN DIEGO, CALIFORNIA 92122

SERIAL NUMBER: 09181671
PATENT NUMBER: 6538151
TITLE: NOVEL MODIFICATIONS OF 2-AMINO-4-(4-FLUOROBENZYLAMINO)- 1-ETHOXYCARBONYLAMINOBENZENE, AND PROCESSES FOR THEIR PREPARATION

FILING DATE: 10/29/1998
ISSUE DATE: 03/25/2003

SEDLEY PYNE, PARALEGAL
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

RECORDATION FORM COVER SHEET
PATENT APPLICATIONS & PA

04-14-2004

102720507

TO THE DIRECTOR OF THE US PATENT AND TRADEMARK OFFICE:
SIR: PLEASE RECORD THE ATTACHED ORIGINAL DOCUMENTS OR C

1. NAME OF CONVEYING PARTY(IES) (ASSIGNORS(S)):
1. Viatris GMBH & Co. KG 4.9.04
2.
3.
4.
5.
6.
7.
8.

ADDITIONAL NAME(S) OF CONVEYING PARTY(IES) ATTACHED? ☐YES ☒NO

2. PARTY(IES) (ASSIGNEE(S)) RECEIVING INTEREST:

NAME: Xcel Pharmaceuticals, Inc.

ADDRESS: 6363 Greenwich Drive, Suite 100, San Diego, CA 92122

ADDITIONAL NAME(S) & ADDRESS(ES) ATTACHED? ☐YES ☒NO

OPR/FINANCE 04 APR -5 AM 7:31

3. NATURE OF CONVEYANCE (DOCUMENT):
(Submit herewith only one document for recordation—multiple copies of same Assignment signed by different inventors is one document)

☒ASSIGNMENT OF ☒WHOLE ☐PART INTEREST
☐ORIGINAL ☒FACSIMILE/PHOTOCOPY
☐CHANGE OF NAME ☐VERIFIED TRANSLATION
☐SECURITY ☐MERGER ☐OTHER:

**EXEC. DATE:** January 24, 2004

EXECUTION DATE(S) ON THE DECLARATION IF FILED HEREWITH: (NOTE: IF DATES ON DECLARATION AND ASSIGNMENT DIFFER SEE ATTY)

4.5 APPL. NO.(S) OR PAT NO.(S). OTHERS ON ADDITIONAL SHEET(S) attached? ☐YES ☒NO

| A. PAT. APP. NO.(S) series code/serial no. | M# | 1st INVENTOR if not in item 1 | B. PATENT NO.(S) | M# | 1st INVENTOR if not in item 1 |
|---|---|---|---|---|---|
| | | | 6,538,151 | 057602-0309221 | Peter Meisel |

5. Name & Address of Party to Whom Correspondence Concerning Document Should be Mailed:

**Pillsbury Winthrop LLP**
**Intellectual Property Group**
11682 El Camino Real, Suite 200
San Diego, CA 92130-2092

6. NUMBER INVOLVED:
APPLNS 0 + PATS 1 = TOTAL = 1

7. AMOUNT OF FEE DUE: (Code 581)
ABOVE TOTAL x $40 = $40

5. ATTY DKT:

| 057602-0309221 | | 8. PLEASE CHARGE TO OUR DEPOSIT ACCOUNT NUMBER: 502212 | | |
|---|---|---|---|---|
| MATTER NO. | CLIENT REF. | UNDER ORDER NO dup. sheet not required | 057602 CLIENT NO. | 0309221 MATTER NO. |

9. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Signature

| 10. Total number of pages including this cover sheet, attachments and document (do not file dup. Cover sheet) | 3 |
|---|---|

Attorney: Richard Blaylock
Reg. No. 43,503 Date: April 9, 2004
TEL: (858) 847-3110 FAX: (858) 509-4010

**FILE WITH PTO RETURN RECEIPT (PAT-103A)**

04/13/2004 GTON11 00000033 502212 6538151
FC:8021 40.00 DA

70060102_1.DOC

PAT-114X 5/03

## ASSIGNMENT OF PATENTS

**WHEREAS,** VIATRIS GmbH & Co. KG, a limited partnership (Kommanditgesellschaft) duly organized under the laws of the Federal Republic of Germany, hereinafter referred to as the "Assignor of Record", is the sole owner of (i) United States Patent Nos. 5,384,330, 5,852,053, 5,849,789, 5,914,425, 6,538,151 and 6,117,900 and (ii) United States Patent Application Serial No. 10/201,296 (published Patent Application No. 20030023111) and No. 10/727,655.

**WHEREAS,** Xcel Pharmaceuticals, Inc., a corporation duly organized and existing under the laws of the State of Delaware, hereinafter referred to as the "Assignee", is desirous of acquiring the entire right, title and interest in the same.

**NOW, THEREFORE,** for good and valuable consideration, the Assignor of Record hereby sells, assigns and transfers unto the Assignee, its successors, assigns and legal representatives, the entire right, title and interests to United States Patent Nos. 5,384,330, 5,852,053, 5,849,789, 5,914,425, 6,538,151 and 6,117,900 and United States Patent Application Serial No. 10/201,296 (published Patent Application No. 20030023111) and No. 10/727,655, and to all continuations, divisions, reissues and substitutes of these United States patents and patent applications, together with the right of priority under the International Convention for the Protection of Industrial Property, Inter-American Convention Relating to Patents, Designs and Industrial Models, and any other international agreements to which the United States of American adheres, and the Assignor of Record herby authorizes and requests the Commissioner of Patents to issue said patents and patent applications to Assignee, for its interest as Assignee, its successors, assigns and legal representatives.

Executed on the date below indicated.

Date: 28 January 2004

VIATRIS GmbH & Co. KG

Signature:

Print Name: Dr. Heinz Kipper

Title: General Manager &
Chief Executive Officer

**No. 583 of the Roll of Deeds of 2004**

I hereby certify, that the above is the true signature, respectively acknowledged in my presence of

Dr. Heinz **Kipper**, born 20.09.1943,
with business address at Weismüllerstraße 45,
60314 Frankfurt am Main,

- who is personally known to me -,

acting on behalf of **VIATRIS GmbH & Co. KG** with registered office at Frankfurt am Main and registered with the Commercial Register of the Local Court Frankfurt under No. HRA 41743.

At the same time I confirm that according to the Commercial Register of the Local Court Frankfurt, which I inspected on 13.01.2004, that

a) Dr. Kipper is managing director of **VIATRIS Verwaltungs GmbH** at Frankfurt am Main (HRB 72689) and is entitled to represent this company solely,

b) VIATRIS Management GmbH is the sole personally liable partner of **VIATRIS GmbH & Co. KG** at Frankfurt am Main (HRA 41743).

The question as to prior involvement within § 3 clause 1 no. 7 German Notarization Act ("BeurkG") was answered in the negative.

Frankfurt am Main, the 29th day of January 2004

Notary

**Kostenberechnung**
Geschäftswert: € 50.000,00

| | |
|---|---|
| 5/20 Gebühr §§ 141, 32, 45/1 KostO | € 33,00 |
| 2x Gebühr § 150 I KostO à € 13,00 | € 26,00 |
| 16 % Mehrwertsteuer | € 9,44 |
| Summe | € 68,44 |

:MCDERMOTT WILL & EMERY L[illegible] COMPANY:4370 LA JOLLA VI[illegible]AGE DRIVE, SUITE 700

**UNITED STATES PATENT AND TRADEMARK OFFICE**

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

*500569201A*

JUNE 18, 2008

PTAS

MCDERMOTT WILL & EMERY LLP
4370 LA JOLLA VILLAGE DRIVE, SUITE 700
SAN DIEGO, CA 92122

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RECORDATION DATE: 06/17/2008 REEL/FRAME: 021109/0083
NUMBER OF PAGES: 8

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: 081117-0125

ASSIGNOR:
XCEL PHARMACEUTICALS, INC. DOC DATE: 03/02/2005

ASSIGNEE:
VALEANT PHARMACEUTICALS NORTH AMERICA
ONE ENTERPRISE
ALISO VIEJO, CALIFORNIA 92656

SERIAL NUMBER: 09181671 FILING DATE: 10/29/1998
PATENT NUMBER: 6538151 ISSUE DATE: 03/25/2003
TITLE: NOVEL MODIFICATIONS OF 2-AMINO-4-(4-FLUOROBENZYLAMINO)- 1-ETHOXYCARBONYLAMINOBENZENE, AND PROCESSES FOR THEIR PREPARATION

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

State of Delaware
Secretary of State
ivision of Corporations
ivered 01:55 PM 03/07/2005
ILED 01:21 PM 03/07/2005
050190697 - 3348132 FILE

# CERTIFICATE OF AMENDMENT OF AMENDED AND RESTATED CERTIFICATE OF INCORPORATION OF XCEL PHARMACEUTICALS, INC.

**March 2, 2005**

Xcel Pharmaceuticals, Inc., a corporation organized and existing under the laws of the State of Delaware (the "Corporation"), hereby certifies as follows:

1. The name of the Corporation is Xcel Pharmaceuticals, Inc. and the date of filing of the original Certificate of Incorporation of this corporation with the Secretary of State of the State of Delaware is January 24, 2001 under the name MJBC Corp. On March 21, 2001, the Corporation filed a Certificate of Amendment to its Certificate of Incorporation. On each of March 29, 2001, June 24, 2002, and March 26, 2003, the Corporation filed an Amended and Restated Certificate of Incorporation. On February 9, 2005, the Corporation filed a Certificate of Amendment to its Certificate of Incorporation and on March 1, 2005, the Corporation filed a Certificate of Merger which Amended and Restated its Certificate of Incorporation.

2. Article FIRST of the Amended and Restated Certificate of Incorporation is hereby amended and, as so amended, shall read in its entirety as follows:

"FIRST. The name of the Corporation is Valeant Pharmaceuticals North America."

3. Pursuant to Section 242 of the General Corporation Law of the State of Delaware, this Certificate of Amendment of Amended and Restated Certificate of Incorporation has been adopted by the Corporation's Board of Directors.

4. Pursuant to Sections 228 and 242 of the General Corporation Law of the State of Delaware, this Certificate of Amendment of Amended and Restated Certificate of Incorporation has been adopted by the written consent of the sole stockholder of the Corporation.

IN WITNESS WHEREOF, Xcel Pharmaceuticals, Inc. has caused this Certificate of Amendment of Amended and Restated Certificate of Incorporation to be signed by its President and Chief Executive Officer, Timothy Tyson, as of the day and year first set forth above.

**XCEL PHARMACEUTICALS, INC.**

Timothy Tyson
President and Chief Executive Officer

## CERTIFICATION REGARDING ASSETS

STATE OF CALIFORNIA §
§
COUNTY OF ORANGE §

Bary G. Bailey, being duly sworn, on oath, deposes and says that he is the Vice President and Treasurer of Xcel Pharmaceuticals, Inc., a Delaware corporation (the "Company") and that the total assets of the Company; as defined in subsection (i) of §503 of the Delaware General Corporation Law, are not less than $10,000,000 as of March 2, 2005.

Name: Bary G. Bailey
Title: Vice President and Treasurer

Sworn to and subscribed before me this 3rd day of March, 2005.

[SEAL]

Notary Public, State of California

My Commission Expires:
June 14, 2007

Printed Name of Notary Public

Dallas_1\4123486\1
41519-9 3/2/2005

PAMELA CHRONISTER LEWIS
Commission # 1424090
Notary Public - California
Orange County
My Comm. Expires Jun 14, 2007

STATE OF NEW YORK )
)SS:
COUNTY OF NEW YORK )

**CERTIFICATE**

On the 7th day of July, 2005, I, Laura Collins, a Notary Public, in and for said State, do hereby certify that the attached document is true and correct copy of the original sealed document provided by the Office of the Secretary for the State of Delaware.

Laura Collins
Notary Public

LAURA COLLINS
Notary Public, State of New York
No. 01CO6018661
Qualified in Nassau County
Commission Expires January 19, 2007

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use POTIGA safely and effectively. See full prescribing information for POTIGA.**

**POTIGA (ezogabine) Tablets**
**Initial U.S. Approval: 2011**

### ----------INDICATIONS AND USAGE----------

POTIGA is a potassium channel opener indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older. (1)

### ---------- DOSAGE AND ADMINISTRATION ----------

- Administer in 3 divided doses daily, with or without food. (2)
- The initial dosage should be 100 mg 3 times daily (300 mg per day) for 1 week. (2)
- Titrate to maintenance dosage by increasing the dosage at weekly intervals by no more than 150 mg per day. (2)
- Optimize effective dosage between 200 mg 3 times daily (600 mg per day) to 400 mg 3 times daily (1,200 mg per day). (2)
- In controlled clinical trials, 400 mg 3 times daily (1,200 mg per day) showed limited improvement compared to 300 mg 3 times daily (900 mg per day) with an increase in adverse reactions and discontinuations. (2)
- When discontinuing POTIGA, reduce the dosage gradually over a period of at least 3 weeks. (2, 5.6)
- Dosing adjustments are required for geriatric patients and patients with moderate to severe renal or hepatic impairment (2)

### ---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 50 mg, 200 mg, 300 mg, and 400 mg. (3)

### ----------CONTRAINDICATIONS----------

None. (4)

### ---------- WARNINGS AND PRECAUTIONS----------

- Urinary retention: Patients should be carefully monitored for urologic symptoms. (5.1)
- Neuropsychiatric symptoms: Monitor for confusional state, psychotic symptoms, and hallucinations. (5.2)
- Dizziness and somnolence: Monitor for dizziness and somnolence.(5.3)
- QT prolongation: QT interval should be monitored in patients taking concomitant medications known to increase the QT interval or with certain heart conditions. (5.4)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.5)

### ---------- ADVERSE REACTIONS ----------

The most common adverse reactions (incidence ≥4% and approximately twice placebo) are dizziness, somnolence, fatigue, confusional state, vertigo, tremor, abnormal coordination, diplopia, disturbance in attention, memory impairment, asthenia, blurred vision, gait disturbance, aphasia, dysarthria, and balance disorder. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

### ----------DRUG INTERACTIONS----------

- Ezogabine plasma levels may be reduced by concomitant administration of phenytoin or carbamazepine. An increase in dosage of POTIGA should be considered when adding phenytoin or carbamazepine. (7.1)
- N-acetyl metabolite of ezogabine may inhibit renal clearance of digoxin, a P-glycoprotein substrate. Monitor digoxin levels. (7.2)

### ---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available. (8.1)
- Pediatric use: Safety and effectiveness in patients under 18 years of age have not been established. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.**

**Revised: 06/2011**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

POTIGA™ is indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older.

## 2 DOSAGE AND ADMINISTRATION

The initial dosage should be 100 mg 3 times daily (300 mg per day). The dosage should be increased gradually at weekly intervals by no more than 50 mg 3 times daily (increase in the daily dose of no more than 150 mg per day) up to a maintenance dosage of 200 to 400 mg 3 times daily (600 to 1,200 mg per day), based on individual patient response and tolerability. This information is summarized in Table 1 under General Dosing. In the controlled clinical trials, 400 mg 3 times daily showed limited evidence of additional improvement in seizure reduction, but an increase in adverse events and discontinuations, compared to the 300 mg 3 times daily dosage. The safety and efficacy of doses greater than 400 mg 3 times daily (1,200 mg per day) have not been examined in controlled trials.

No adjustment in dosage is required for patients with mild renal or hepatic impairment (see General Dosing, Table 1). Dosage adjustment is required in patients with moderate and greater renal or hepatic impairment (see Dosing in Specific Populations, Table 1).

POTIGA should be given orally in 3 equally divided doses daily, with or without food.

POTIGA Tablets should be swallowed whole.

If POTIGA is discontinued, the dosage should be gradually reduced over a period of at least 3 weeks, unless safety concerns require abrupt withdrawal.

**Table 1: Dosing Recommendations**

| Specific Population | Initial Dose | Titration | Maximum Dose |
|---|---|---|---|
| **General Dosing** | | | |
| General population (including patients with mild renal or hepatic impairment) | 100 mg 3 times daily (300 mg per day) | Increase by no more than 50 mg 3 times daily, at weekly intervals | 400 mg 3 times daily (1,200 mg per day) |
| **Dosing in Specific Populations** | | | |
| Geriatrics (patients >65 years) | 50 mg 3 times daily (150 mg per day) | Increase by no more than 50 mg 3 times daily, at weekly intervals | 250 mg 3 times daily (750 mg per day) |
| Renal impairment (patients with CrCL <50 mL per min or end-stage renal disease on | 50 mg 3 times daily (150 mg per day) | | 200 mg 3 times daily (600 mg per day) |

| | | | |
|---|---|---|---|
| dialysis) | | | |
| Hepatic impairment (patients with Child-Pugh >7-9) | 50 mg 3 times daily (150 mg per day) | | 250 mg 3 times daily (750 mg per day) |
| Hepatic impairment (patients with Child-Pugh >9) | 50 mg 3 times daily (150 mg per day) | | 200 mg 3 times daily (600 mg per day) |

## 3 DOSAGE FORMS AND STRENGTHS

50 mg, purple, round, film-coated tablets debossed with "RTG 50" on one side.
200 mg, yellow, oblong, film-coated tablets debossed with "RTG-200" on one side.
300 mg, green, oblong, film-coated tablets debossed with "RTG-300" on one side.
400 mg, purple, oblong, film-coated tablets debossed with "RTG-400" on one side.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Urinary Retention

POTIGA caused urinary retention in clinical trials. Urinary retention was generally reported within the first 6 months of treatment, but was also observed later. Urinary retention was reported as an adverse event in 29 of 1,365 (approximately 2%) patients treated with POTIGA in the open-label and placebo-controlled epilepsy database *[see Clinical Studies (14)]*. Of these 29 patients, 4 (14%) required catheterization, with post-voiding residuals of up to 1,500 mL. Following discontinuation of POTIGA, all 4 patients who required catheterization for urinary retention were able to void spontaneously; however, 1 of the 4 patients also required continued intermittent self-catheterization following discontinuation of POTIGA. Hydronephrosis occurred in 2 patients, one of whom had associated renal function impairment that resolved upon discontinuation of POTIGA. Hydronephrosis was not reported in placebo patients.

In the placebo-controlled epilepsy trials, "urinary retention," "urinary hesitation," and "dysuria" were reported in 0.9%, 2.2%, and 2.3% of patients on POTIGA, respectively, and in 0.5%, 0.9%, and 0.7% of patients on placebo, respectively.

Because of the increased risk of urinary retention on POTIGA, urologic symptoms should be carefully monitored. Closer monitoring is recommended for patients who have other risk factors for urinary retention (e.g., benign prostatic hyperplasia [BPH]), patients who are unable to communicate clinical symptoms (e.g., cognitively impaired patients), or patients who use concomitant medications that may affect voiding (e.g., anticholinergics). In these patients, a comprehensive evaluation of urologic symptoms prior to and during treatment with POTIGA may be appropriate.

## 5.2 Neuro-Psychiatric Symptoms

Confusional state, psychotic symptoms, and hallucinations were reported more frequently as adverse reactions in patients treated with POTIGA than in those treated with placebo in placebo-controlled epilepsy trials (see Table 2). Discontinuations resulting from these reactions were more common in the drug-treated group (see Table 2). These effects were dose-related and generally appeared within the first 8 weeks of treatment. Half of the patients in the controlled trials who discontinued POTIGA due to hallucinations or psychosis required hospitalization. Approximately two-thirds of patients with psychosis in controlled trials had no prior psychiatric history. The psychiatric symptoms in the vast majority of patients in both controlled and open-label trials resolved within 7 days of discontinuation of POTIGA. Rapid titration at greater than the recommended doses appeared to increase the risk of psychosis and hallucinations.

**Table 2. Major Neuro-Psychiatric Symptoms in Placebo-Controlled Epilepsy Trials**

| | Number (%) With Adverse Reaction | | Number (%) Discontinuing | |
|---|---|---|---|---|
| Adverse Reaction | POTIGA (n = 813) | Placebo (n = 427) | POTIGA (n = 813) | Placebo (n = 427) |
| Confusional state | 75 (9%) | 11 (3%) | 32 (4%) | 4 (<1%) |
| Psychosis | 9 (1%) | 0 | 6 (<1%) | 0 |
| Hallucinations[a] | 14 (2%) | 2 (<1%) | 6 (<1%) | 0 |

[a] Hallucinations includes visual, auditory, and mixed hallucinations.

## 5.3 Dizziness and Somnolence

POTIGA causes dose-related increases in dizziness and somnolence *[see Adverse Reactions (6.1)]*. In placebo-controlled trials in patients with epilepsy, dizziness was reported in 23% of patients treated with POTIGA and 9% of patients treated with placebo. Somnolence was reported in 22% of patients treated with POTIGA and 12% of patients treated with placebo. In these trials 6% of patients on POTIGA and 1.2% on placebo discontinued treatment because of dizziness; 3% of patients on POTIGA and <1.0% on placebo discontinued because of somnolence.

Most of these adverse reactions were mild to moderate in intensity and occurred during the titration phase. For those patients continued on POTIGA, dizziness and somnolence appeared to diminish with continued use.

## 5.4 QT Interval Effect

A study of cardiac conduction showed that POTIGA produced a mean 7.7-msec QT prolongation in healthy volunteers titrated to 400 mg 3 times daily. The QT-prolonging effect occurred within 3 hours. The QT interval should be monitored when POTIGA is prescribed with medicines known to increase QT interval and in patients with known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia *[see Clinical Pharmacology (12.2)]*.

## 5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including POTIGA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive-therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% confidence interval [CI]: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanism of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

**Table 3. Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis**

| Indication | Placebo Patients With Events per 1,000 Patients | Drug Patients With Events per 1,000 Patients | Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients | Risk Difference: Additional Drug Patients With Events per 1,000 Patients |
|---|---|---|---|---|
| Epilepsy | 1.0 | 3.4 | 3.5 | 2.4 |
| Psychiatric | 5.7 | 8.5 | 1.5 | 2.9 |
| Other | 1.0 | 1.8 | 1.9 | 0.9 |
| Total | 2.4 | 4.3 | 1.8 | 1.9 |

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for epilepsy and psychiatric indications.

Anyone considering prescribing POTIGA or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression; any unusual changes in mood or behavior; or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

### 5.6 Withdrawal Seizures

As with all AEDs, when POTIGA is discontinued, it should be withdrawn gradually when possible to minimize the potential of increased seizure frequency *[see Dosage and Administration (2)]*. The dosage of POTIGA should be reduced over a period of at least 3 weeks, unless safety concerns require abrupt withdrawal.

## 6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label:

- Urinary retention *[see Warnings and Precautions (5.1)]*
- Neuro-psychiatric symptoms *[see Warnings and Precautions (5.2)]*
- Dizziness and somnolence *[see Warnings and Precautions (5.3)]*
- QT interval effect *[see Warnings and Precautions (5.4)]*
- Suicidal behavior and ideation *[see Warnings and Precautions (5.5)]*
- Withdrawal seizures *[see Warnings and Precautions (5.6)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions and for varying durations, adverse reaction frequencies observed in the clinical trials of a drug cannot be directly compared with frequencies in the clinical trials of another drug and may not reflect the frequencies observed in practice.

POTIGA was administered as adjunctive therapy to 1,365 patients with epilepsy in all controlled and uncontrolled clinical studies during the premarketing development. A total of 801 patients were treated for at least 6 months, 585 patients were treated for 1 year or longer, and 311 patients were treated for at least 2 years.

Adverse Reactions Leading to Discontinuation in All Controlled Clinical Studies:

In the 3 randomized, double-blind, placebo-controlled studies, 199 of 813 patients (25%) receiving POTIGA and 45 of 427 patients (11%) receiving placebo discontinued treatment because of adverse reactions. The most common adverse reactions leading to withdrawal in

patients receiving POTIGA were dizziness (6%), confusional state (4%), fatigue (3%), and somnolence (3%).

Common Adverse Reactions in All Controlled Clinical Studies: Overall, the most frequently reported adverse reactions in patients receiving POTIGA (≥4% and occurring approximately twice the placebo rate) were dizziness (23%), somnolence (22%), fatigue (15%), confusional state (9%), vertigo (8%), tremor (8%), abnormal coordination (7%), diplopia (7%), disturbance in attention (6%), memory impairment (6%), asthenia (5%), blurred vision (5%), gait disturbance (4%), aphasia (4%), dysarthria (4%), and balance disorder (4%). In most cases the reactions were of mild or moderate intensity.

**Table 4. Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Partial Onset Seizures (Adverse reactions in at least 2% of patients treated with POTIGA in any treatment group and numerically more frequent than in the placebo group.)**

| | | POTIGA | | | |
|---|---|---|---|---|---|
| | Placebo | 600 mg/day | 900 mg/day | 1,200 mg/day | All |
| Body System/ Adverse Reaction | (N = 427) % | (N = 281) % | (N = 273) % | (N = 259) % | (N = 813) % |
| Eye | | | | | |
| Diplopia | 2 | 8 | 6 | 7 | 7 |
| Blurred vision | 2 | 2 | 4 | 10 | 5 |
| Gastrointestinal | | | | | |
| Nausea | 5 | 6 | 6 | 9 | 7 |
| Constipation | 1 | 1 | 4 | 5 | 3 |
| Dyspepsia | 2 | 3 | 2 | 3 | 2 |
| General | | | | | |
| Fatigue | 6 | 16 | 15 | 13 | 15 |
| Asthenia | 2 | 4 | 6 | 4 | 5 |
| Infections and infestations | | | | | |
| Influenza | 2 | 4 | 1 | 5 | 3 |
| Investigations | | | | | |
| Weight increased | 1 | 2 | 3 | 3 | 3 |
| Nervous system | | | | | |
| Dizziness | 9 | 15 | 23 | 32 | 23 |
| Somnolence | 12 | 15 | 25 | 27 | 22 |
| Memory impairment | 3 | 3 | 6 | 9 | 6 |
| Tremor | 3 | 3 | 10 | 12 | 8 |
| Vertigo | 2 | 8 | 8 | 9 | 8 |
| Abnormal coordination | 3 | 5 | 5 | 12 | 7 |
| Disturbance in attention | <1 | 6 | 6 | 7 | 6 |

| | | | | | |
|---|---|---|---|---|---|
| Gait disturbance | 1 | 2 | 5 | 6 | 4 |
| Aphasia | <1 | 1 | 3 | 7 | 4 |
| Dysarthria | <1 | 4 | 2 | 8 | 4 |
| Balance disorder | <1 | 3 | 3 | 5 | 4 |
| Paresthesia | 2 | 3 | 2 | 5 | 3 |
| Amnesia | <1 | <1 | 3 | 3 | 2 |
| Dysphasia | <1 | 1 | 1 | 3 | 2 |
| Psychiatric | | | | | |
| Confusional state | 3 | 4 | 8 | 16 | 9 |
| Anxiety | 2 | 3 | 2 | 5 | 3 |
| Disorientation | <1 | <1 | <1 | 5 | 2 |
| Psychotic disorder | 0 | 0 | <1 | 2 | <1 |
| Renal and urinary | | | | | |
| Dysuria | <1 | 1 | 2 | 4 | 2 |
| Urinary hesitation | <1 | 2 | 1 | 4 | 2 |
| Hematuria | <1 | 2 | 1 | 2 | 2 |
| Chromaturia | <1 | <1 | 2 | 3 | 2 |

Other adverse reactions reported in these 3 studies in <2% of patients treated with POTIGA and numerically greater than placebo were increased appetite, hallucinations, myoclonus, peripheral edema, hypokinesia, dry mouth, dysphagia, hyperhydrosis, urinary retention, malaise, and increased liver enzymes.

Most of the adverse reactions appear to be dose related (especially those classified as psychiatric and nervous system symptoms), including dizziness, somnolence, confusional state, tremor, abnormal coordination, memory impairment, blurred vision, gait disturbance, aphasia, balance disorder, constipation, dysuria, and chromaturia.

POTIGA was associated with dose-related weight gain, with mean weight increasing by 0.2, 1.2, 1.6, and 2.7 kg in the placebo, 600-mg/day, 900-mg/day, and 1,200-mg/day groups, respectively.

Additional Adverse Reactions Observed During All Phase 2 and 3 Clinical Trials: Following is a list of adverse reactions reported by patients treated with POTIGA during all clinical trials: rash, nystagmus, dyspnea, leukopenia, muscle spasms, alopecia, nephrolithiasis, syncope, neutropenia, thrombocytopenia, euphoric mood, renal colic, coma, encephalopathy.

Comparison of Gender, Age, and Race: The overall adverse reaction profile of POTIGA was similar for females and males.

There are insufficient data to support meaningful analyses of adverse reactions by age or race. Approximately 86% of the population studied was Caucasian, and 0.8% of the population was older than 65 years.

## 7 DRUG INTERACTIONS

### 7.1 Antiepileptic Drugs

The potentially significant interactions between POTIGA and concomitant AEDs are summarized in Table 5.

**Table 5. Significant Interactions Between POTIGA and Concomitant Antiepileptic Drugs**

| AED | Dose of AED (mg/day) | Dose of POTIGA (mg/day) | Influence of POTIGA on AED | Influence of AED on POTIGA | Dosage Adjustment |
|---|---|---|---|---|---|
| Carbamazepine[a,b] | 600-2,400 | 300-1,200 | None | 31% decrease in AUC, 23% decrease in $C_{max}$ | consider an increase in dosage of POTIGA when adding carbamazepine[c] |
| Phenytoin[a,b] | 120-600 | 300-1,200 | None | 34% decrease in AUC, 18% decrease in $C_{max}$ | consider an increase in dosage of POTIGA when adding phenytoin[c] |

[a] Based on results of a Phase 2 study.

[b] Inducer for uridine 5'-diphosphate (UDP)-glucuronyltransferases (UGTs).

[c] A decrease in dosage of POTIGA should be considered when carbamazepine or phenytoin is discontinued.

*[See Clinical Pharmacology (12.3)]*

### 7.2 Digoxin

Data from an *in vitro* study showed that the N-acetyl metabolite of ezogabine (NAMR) inhibited P-glycoprotein–mediated transport of digoxin in a concentration-dependent manner, indicating that NAMR may inhibit renal clearance of digoxin. Administration of POTIGA at therapeutic doses may increase digoxin serum concentrations. Serum levels of digoxin should be monitored *[see Clinical Pharmacology (12.3)]*.

### 7.3 Alcohol

Alcohol increased systemic exposure to POTIGA. Patients should be advised of possible worsening of ezogabine's general dose-related adverse reactions if they take POTIGA with alcohol *[see Clinical Pharmacology (12.3)]*.

### 7.4 Laboratory Tests

Ezogabine has been shown to interfere with clinical laboratory assays of both serum and urine bilirubin, which can result in falsely elevated readings.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. POTIGA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, doses associated with maternal plasma exposures (AUC) to ezogabine and its major circulating metabolite, NAMR, similar to or below those expected in humans at the maximum recommended human dose (MRHD) of 1,200 mg/day produced developmental toxicity when administered to pregnant rats and rabbits. The maximum doses evaluated were limited by maternal toxicity (acute neurotoxicity).

Treatment of pregnant rats with ezogabine (oral doses of up to 46 mg/kg/day) throughout organogenesis increased the incidences of fetal skeletal variations. The no-effect dose for embryo-fetal toxicity in rats (21 mg/kg/day) was associated with maternal plasma exposures (AUC) to ezogabine and NAMR less than those in humans at the MRHD. Treatment of pregnant rabbits with ezogabine (oral doses of up to 60 mg/kg/day) throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal skeletal variations. The no-effect dose for embryo-fetal toxicity in rabbits (12 mg/kg/day) was associated with maternal plasma exposures to ezogabine and NAMR less than those in humans at the MRHD.

Administration of ezogabine (oral doses of up to 61.9 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased pre- and postnatal mortality, decreased body weight gain, and delayed reflex development in the offspring. The no-effect dose for pre- and postnatal developmental effects in rats (17.8 mg/kg/day) was associated with maternal plasma exposures to ezogabine and NAMR less than those in humans at the MRHD.

Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to POTIGA, physicians are advised to recommend that pregnant patients taking POTIGA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website www.aedpregnancyregistry.org.

### 8.2 Labor and Delivery

The effects of POTIGA on labor and delivery in humans are unknown.

### 8.3 Nursing Mothers

It is not known whether ezogabine is excreted in human milk. However, ezogabine and/or its metabolites are present in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from POTIGA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

The safety and effectiveness of POTIGA in patients under 18 years of age have not been established.

In juvenile animal studies, increased sensitivity to acute neurotoxicity and urinary bladder toxicity was observed in young rats compared to adults. In studies in which rats were dosed starting on postnatal day 7, ezogabine-related mortality, clinical signs of neurotoxicity, and renal

and urinary tract toxicities were observed at doses ≥2 mg/kg/day. The no-effect level was associated with plasma ezogabine exposures (AUC) less than those expected in human adults at the MRHD of 1,200 mg/day. In studies in which dosing began on postnatal day 28, acute central nervous system effects, but no apparent renal or urinary tract effects, were observed at doses of up to 30 mg/kg/day. These doses were associated with plasma ezogabine exposures less than those achieved clinically at the MRHD.

### 8.5 Geriatric Use

There were insufficient numbers of elderly patients enrolled in partial-onset seizure controlled trials (n = 8 patients on ezogabine) to determine the safety and efficacy of POTIGA in this population. Dosage adjustment is recommended in patients aged 65 years and older *[see Dosage and Administration (2), Clinical Pharmacology (12.3)]*.

POTIGA may cause urinary retention. Elderly men with symptomatic BPH may be at increased risk for urinary retention.

### 8.6 Patients With Renal Impairment

Dosage adjustment is recommended for patients with creatinine clearance <50 mL/min or patients with end-stage renal disease (ESRD) receiving dialysis treatments *[see Dosage and Administration (2), Clinical Pharmacology (12.3)]*.

### 8.7 Patients With Hepatic Impairment

No dosage adjustment is required for patients with mild hepatic impairment.

In patients with moderate or severe hepatic impairment, the initial and maintenance dosage of POTIGA should be reduced *[see Dosage and Administration (2), Clinical Pharmacology (12.3)]*.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.2 Abuse

A human abuse potential study was conducted in recreational sedative-hypnotic abusers (n = 36) in which single oral doses of ezogabine (300 [n = 33], 600 [n = 34], 900 mg [n =6]), the sedative-hypnotic alprazolam (1.5 and 3.0 mg), and placebo were administered. Euphoria-type subjective responses to the 300- and 600-mg doses of ezogabine were statistically different from placebo but statistically indistinguishable from those produced by either dose of alprazolam. Adverse events reported following administration of single oral doses of 300, 600, and 900 mg ezogabine given without titration included euphoric mood (18%, 21%, and 33%, respectively; 8% from placebo), hallucination (0%, 0%, and 17%, respectively; 0% from placebo) and somnolence (18%, 15%, and 67%, respectively; 15% from placebo).

In Phase 1 clinical studies, healthy individuals who received oral ezogabine (200 to 1,650 mg) reported euphoria (8.5%), feeling drunk (5.5%), hallucination (5.1%), disorientation (1.7%), and feeling abnormal (1.5%).

In the 3 randomized, double-blind, placebo-controlled Phase 2 and 3 clinical studies, patients with partial seizures who received oral ezogabine (300 to 1,200 mg) reported euphoric

mood (0.5%) and feeling drunk (0.9%), while those who received placebo did not report either adverse event (0%).

### 9.3 Dependence

There are no adequate data to assess the ability of ezogabine to induce symptoms of withdrawal indicative of physical dependence. However, the ability of ezogabine to produce psychological dependence is suggested by adverse event reports of euphoric mood (18% [6 of 33 subjects] to 33% [2 of 6 subjects]) in sedative-hypnotic abusers in the human abuse potential study and adverse event reports of euphoria (8.5%) in healthy individuals who participated in Phase 1 studies.

## 10 OVERDOSAGE

### 10.1 Signs, Symptoms, and Laboratory Findings

There is limited experience of overdose with POTIGA. Total daily doses of POTIGA over 2,500 mg were reported during clinical trials. In addition to adverse reactions seen at therapeutic doses, symptoms reported with POTIGA overdose included agitation, aggressive behavior, and irritability. There were no reported sequelae.

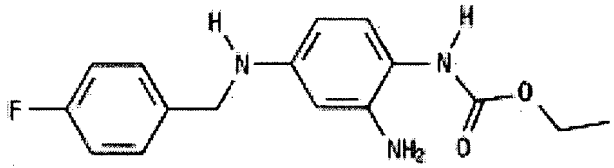
In an abuse potential study, cardiac arrhythmia (asystole or ventricular tachycardia) occurred in 2 volunteers within 3 hours of receiving a single 900-mg dose of POTIGA. The arrhythmias spontaneously resolved and both volunteers recovered without sequelae.

### 10.2 Management of Overdose

There is no specific antidote for overdose with POTIGA. In the event of overdose, standard medical practice for the management of any overdose should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with POTIGA.

## 11 DESCRIPTION

The chemical name of ezogabine is N-[2-amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, and it has the following structure:




The empirical formula is $C_{16}H_{18}FN_3O_2$, representing a molecular weight of 303.3. Ezogabine is a white to slightly colored, odorless, tasteless, crystalline powder. At room temperature, ezogabine is practically insoluble in aqueous media at pH values above 4, while the solubility is higher in polar organic solvents. At gastric pH, ezogabine is sparingly soluble in water (about 16 g/L). The pKa is approximately 3.7 (basic).

POTIGA is supplied for oral administration as 50-, 200-, 300-, and 400-mg film-coated immediate-release tablets. Each tablet contains the labeled amount of ezogabine and the

following inactive ingredients: carmine (50- and 400-mg tablets), croscarmellose sodium, FD&C Blue No. 2 (50-, 300-, and 400-mg tablets), hypromellose, iron oxide yellow (200- and 300-mg tablets), magnesium stearate, microcrystalline cellulose, polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism by which ezogabine exerts its therapeutic effects has not been fully elucidated. *In vitro* studies indicate that ezogabine enhances transmembrane potassium currents mediated by the KCNQ (Kv7.2 to 7.5) family of ion channels. By activating KCNQ channels, ezogabine is thought to stabilize the resting membrane potential and reduce brain excitability. *In vitro* studies suggest that ezogabine may also exert therapeutic effects through augmentation of GABA-mediated currents.

### 12.2 Pharmacodynamics

The QTc prolongation risk of POTIGA was evaluated in healthy subjects. In a randomized, double-blind, active- and placebo-controlled parallel-group study, 120 healthy subjects (40 in each group) were administered POTIGA titrated up to the final dose of 400 mg 3 times daily, placebo, and placebo and moxifloxacin (on day 22). After 22 days of dosing, the maximum mean (upper 1-sided, 95% CI) increase of baseline- and placebo-adjusted QTc interval based on Fridericia correction method (QTcF) was 7.7 msec (11.9 msec) and was observed at 3 hours after dosing in subjects who achieved 1,200 mg/day. No effects on heart rate, PR, or QRS intervals were noted.

Patients who are prescribed POTIGA with medicines known to increase QT interval or who have known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia should be observed closely *[see Warnings and Precautions (5.4)]*.

### 12.3 Pharmacokinetics

The pharmacokinetic profile is approximately linear in daily doses between 600 and 1,200 mg in patients with epilepsy, with no unexpected accumulation following repeated administration. The pharmacokinetics of ezogabine are similar in healthy volunteers and patients with epilepsy.

Absorption: After both single and multiple oral doses, ezogabine is rapidly absorbed with median time to maximum plasma concentration ($T_{max}$) values generally between 0.5 and 2 hours. Absolute oral bioavailability of ezogabine relative to an intravenous dose of ezogabine is approximately 60%. High-fat food does not affect the extent to which ezogabine is absorbed based on plasma AUC values, but it increases peak concentration ($C_{max}$) by approximately 38% and delays $T_{max}$ by 0.75 hour.

POTIGA can be taken with or without food.

Distribution: Data from *in vitro* studies indicate that ezogabine and NAMR are approximately 80% and 45% bound to plasma protein, respectively. Clinically significant

interactions with other drugs through displacement from proteins are not anticipated. The steady-state volume of distribution of ezogabine is 2 to 3 L/kg following intravenous dosing, suggesting that ezogabine is well distributed in the body.

Metabolism: Ezogabine is extensively metabolized primarily via glucuronidation and acetylation in humans. A substantial fraction of the ezogabine dose is converted to inactive N-glucuronides, the predominant circulating metabolites in humans. Ezogabine is also metabolized to NAMR that is also subsequently glucuronidated. NAMR has antiepileptic activity, but it is less potent than ezogabine in animal seizure models. Additional minor metabolites of ezogabine are an N-glucoside of ezogabine and a cyclized metabolite believed to be formed from NAMR. *In vitro* studies using human biomaterials showed that the N-acetylation of ezogabine was primarily carried out by NAT2, while glucuronidation was primarily carried out by UGT1A4, with contributions by UGT1A1, UGT1A3, and UGT1A9.

*In vitro* studies showed no evidence of oxidative metabolism of ezogabine or NAMR by cytochrome P450 enzymes. Coadministration of ezogabine with medications that are inhibitors or inducers of cytochrome P450 enzymes is therefore unlikely to affect the pharmacokinetics of ezogabine or NAMR.

Elimination: Results of a mass balance study suggest that renal excretion is the major route of elimination for ezogabine and NAMR. About 85% of the dose was recovered in the urine, with the unchanged parent drug and NAMR accounting for 36% and 18% of the administered dose, respectively, and the total N-glucuronides of ezogabine and NAMR accounting for 24% of the administered dose. Approximately 14% of the radioactivity was recovered in the feces, with unchanged ezogabine accounting for 3% of the total dose. Average total recovery in both urine and feces within 240 hours after dosing is approximately 98%.

Ezogabine and its N-acetyl metabolite have similar elimination half-lives ($t_{½}$) of 7 to 11 hours. The clearance of ezogabine following intravenous dosing was approximately 0.4 to 0.6 L/hr/kg. Ezogabine is actively secreted into the urine.

Specific Populations: *Race:* No study has been conducted to investigate the impact of race on pharmacokinetics of ezogabine. A population pharmacokinetic analysis comparing Caucasians and non-Caucasians (predominately African American and Hispanic patients) showed no significant pharmacokinetic difference. No adjustment of the ezogabine dose for race is recommended.

*Gender:* The impact of gender on the pharmacokinetics of ezogabine was examined following a single dose of POTIGA to healthy young (aged 21 to 40 years) and elderly (aged 66 to 82 years) subjects. The AUC values were approximately 20% higher in young females compared to young males and approximately 30% higher in elderly females compared to elderly males. The $C_{max}$ values were approximately 50% higher in young females compared to young males and approximately 100% higher in elderly females compared to elderly males. There was no gender difference in weight-normalized clearance. Overall, no adjustment of the dosage of POTIGA is recommended based on gender.

*Pediatric Patients:* The pharmacokinetics of ezogabine in pediatric patients have not been investigated.

*Geriatric:* The impact of age on the pharmacokinetics of ezogabine was examined following a single dose of ezogabine to healthy young (aged 21 to 40 years) and elderly (aged 66 to 82 years) subjects. Systemic exposure (AUC) of ezogabine was approximately 40% to 50% higher and terminal half-life was prolonged by approximately 30% in the elderly compared to the younger subjects. The peak concentration ($C_{max}$) was similar to that observed in younger subjects. A dosage reduction in the elderly is recommended *[see Dosage and Administration (2), Use in Specific Populations (8.5)]*.

*Renal Impairment:* The pharmacokinetics of ezogabine were studied following a single 100-mg dose of POTIGA in subjects with normal (CrCL >80 ml/min), mild (CrCL ≥50 to <80 mL/min), moderate (CrCL ≥30 to <50 mL/min), or severe renal impairment (CrCL <30 mL/min) (n = 6 in each cohort) and in subjects with ESRD requiring hemodialysis (n = 6). The ezogabine AUC was increased by approximately 30% in patients with mild renal impairment and doubled in patients with moderate impairment to ESRD (CrCL <50 mL/min) relative to healthy subjects. Similar increases in NAMR exposure were observed in the various degrees of renal impairment. The effect of hemodialysis on ezogabine clearance has not been established. Dosage reduction is recommended for patients with creatinine clearance <50 mL/min and for patients with ESRD receiving dialysis *[see Dosage and Administration (2), Use in Specific Populations (8.6)]*.

*Hepatic Impairment:* The pharmacokinetics of ezogabine were studied following a single 100-mg dose of POTIGA in subjects with normal, mild (Child-Pugh score 5 to 6), moderate (Child-Pugh score 7 to 9), or severe hepatic (Child-Pugh score >9) impairment (n = 6 in each cohort). Relative to healthy subjects, ezogabine AUC was not affected by mild hepatic impairment, but was increased by approximately 50% in subjects with moderate hepatic impairment and doubled in subjects with severe hepatic impairment. There was an increase of approximately 30% in exposure to NAMR in patients with moderate to severe impairment. Dosage reduction is recommended for patients with moderate and severe hepatic impairment *[see Dosage and Administration (2), Use in Specific Populations (8.7)]*.

Drug Interactions: *In vitro* studies using human liver microsomes indicated that ezogabine does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Inhibition of CYP2B6 by ezogabine has not been evaluated. In addition, *in vitro* studies in human primary hepatocytes showed that ezogabine and NAMR did not induce CYP1A2 or CYP3A4/5 activity. Therefore, ezogabine is unlikely to affect the pharmacokinetics of substrates of the major cytochrome P450 isoenzymes through inhibition or induction mechanisms.

Ezogabine is neither a substrate nor an inhibitor of P-glycoprotein, an efflux transporter. NAMR is a P-glycoprotein inhibitor. Data from an *in vitro* study showed that NAMR inhibited P-glycoprotein–mediated transport of digoxin in a concentration-dependent manner, indicating

that NAMR may inhibit renal clearance of digoxin. Administration of POTIGA at therapeutic doses may increase digoxin serum concentrations *[see Drug Interactions (7.2)]*.

*Interactions with Antiepileptic Drugs:* The interactions between POTIGA and concomitant AEDs are summarized in Table 6.

**Table 6. Interactions Between POTIGA and Concomitant Antiepileptic Drugs**

| AED | Dose of AED (mg/day) | Dose of POTIGA (mg/day) | Influence of POTIGA on AED | Influence of AED on POTIGA | Dosage Adjustment |
|---|---|---|---|---|---|
| Carbamazepine[a,b] | 600-2,400 | 300-1,200 | None | 31% decrease in AUC, 23% decrease in $C_{max}$, 28% increase in clearance | consider an increase in dosage of POTIGA when adding carbamazepine[c] |
| Phenytoin[a,b] | 120-600 | 300-1,200 | None | 34% decrease in AUC, 18% decrease in $C_{max}$, 33% increase in clearance | consider an increase in dosage of POTIGA when adding phenytoin[c] |
| Topiramate[a] | 250-1,200 | 300-1,200 | None | None | None |
| Valproate[a] | 750-2,250 | 300-1,200 | None | None | None |
| Phenobarbital | 90 | 600 | None | None | None |
| Lamotrigine | 200 | 600 | 18% decrease in AUC, 22% increase in clearance | None | None |
| Others[d] | | | None | None | None |

[a] Based on results of a Phase 2 study.

[b] Inducer for uridine 5'-diphosphate (UDP)-glucuronyltransferases (UGTs).

[c] A decrease in dose of POTIGA should be considered when carbamazepine or phenytoin is discontinued.

[d] Zonisamide, valproic acid, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, pregabalin, topiramate, clobazam, and lamotrigine, based on a population pharmacokinetic analysis using pooled data from Phase 3 clinical trials.

*Oral Contraceptives:* In one study examining the potential interaction between ezogabine (150 mg 3 times daily for 3 days) and the combination oral contraceptive norgestrel/ethinyl estradiol (0.3 mg/0.03 mg) tablets in 20 healthy females, no significant alteration in the pharmacokinetics of either drug was observed.

In a second study examining the potential interaction of repeated ezogabine dosing (250 mg 3 times daily for 14 days) and the combination oral contraceptive norethindrone/ethinyl estradiol (1 mg/0.035 mg) tablets in 25 healthy females, no significant alteration in the pharmacokinetics of either drug was observed.

*Alcohol:* In a healthy volunteer study, the coadministration of ethanol 1g/kg (5 standard alcohol drinks) over 20 minutes and ezogabine (200 mg) resulted in an increase in the ezogabine $C_{max}$ and AUC by 23% and 37%, respectively *[see Drug Interactions (7.3)]*.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In a one-year neonatal mouse study of ezogabine (2 single-dose oral administrations of up to 96 mg/kg on postnatal days 8 and 15), a dose-related increase in the frequency of lung neoplasms (bronchioalveolar carcinoma and/or adenoma) was observed in treated males. No evidence of carcinogenicity was observed in rats following oral administration of ezogabine (oral gavage doses of up to 50 mg/kg/day) for 2 years. Plasma exposure (AUC) to ezogabine at the highest doses tested was less than that in humans at the maximum recommended human dose (MRHD) of 1,200 mg/day.

Mutagenesis: Highly purified ezogabine was negative in the *in vitro* Ames assay, the *in vitro* Chinese hamster ovary (CHO) *Hprt* gene mutation assay, and the *in vivo* mouse micronucleus assay. Ezogabine was positive in the *in vitro* chromosomal aberration assay in human lymphocytes. The major circulating metabolite of ezogabine, NAMR, was negative in the *in vitro* Ames assay, but positive in the *in vitro* chromosomal aberration assay in CHO cells.

Impairment of Fertility: Ezogabine had no effect on fertility, general reproductive performance, or early embryonic development when administered to male and female rats at doses of up to 46.4 mg/kg/day (associated with a plasma ezogabine exposure [AUC] less than that in humans at the MRHD) prior to and during mating, and continuing in females through gestation day 7.

## 14 CLINICAL STUDIES

The efficacy of POTIGA as adjunctive therapy in partial-onset seizures was established in 3 multicenter, randomized, double-blind, placebo-controlled studies in 1,239 adult patients. The primary endpoint consisted of the percent change in seizure frequency from baseline in the double-blind treatment phase.

Patients enrolled in the studies had partial onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant AEDs, with or without concomitant vagus nerve stimulation. More than 75% of patients were taking 2 or more concomitant AEDs. During an 8-week baseline period, patients experienced at least 4 partial onset seizures per 28 days on average with no seizure-free period exceeding 3 to 4 weeks. Patients had a mean duration of epilepsy of 22 years. Across the 3 studies, the median baseline seizure frequency ranged from 8 to 12 seizures per month. The criteria for statistical significance was $P<0.05$.

Patients were randomized to the total daily maintenance dosages of 600 mg/day, 900 mg/day, or 1,200 mg/day, each administered in 3 equally divided doses. During the titration phase of all 3 studies, treatment was initiated at 300 mg/day (100 mg 3 times per day) and increased in weekly increments of 150 mg/day to the target maintenance dosage.

Figure 1 shows the median percent reduction in 28-day seizure frequency (baseline to double-blind phase) as compared with placebo across all 3 studies. A statistically significant effect was observed with POTIGA at doses of 600 mg/day (Study 1), at 900 mg/day (Studies 1 and 3), and at 1,200 mg/day (Studies 2 and 3).

**Figure 1. Median Percent Reduction From Baseline in Seizure Frequency per 28 Days by Dose**

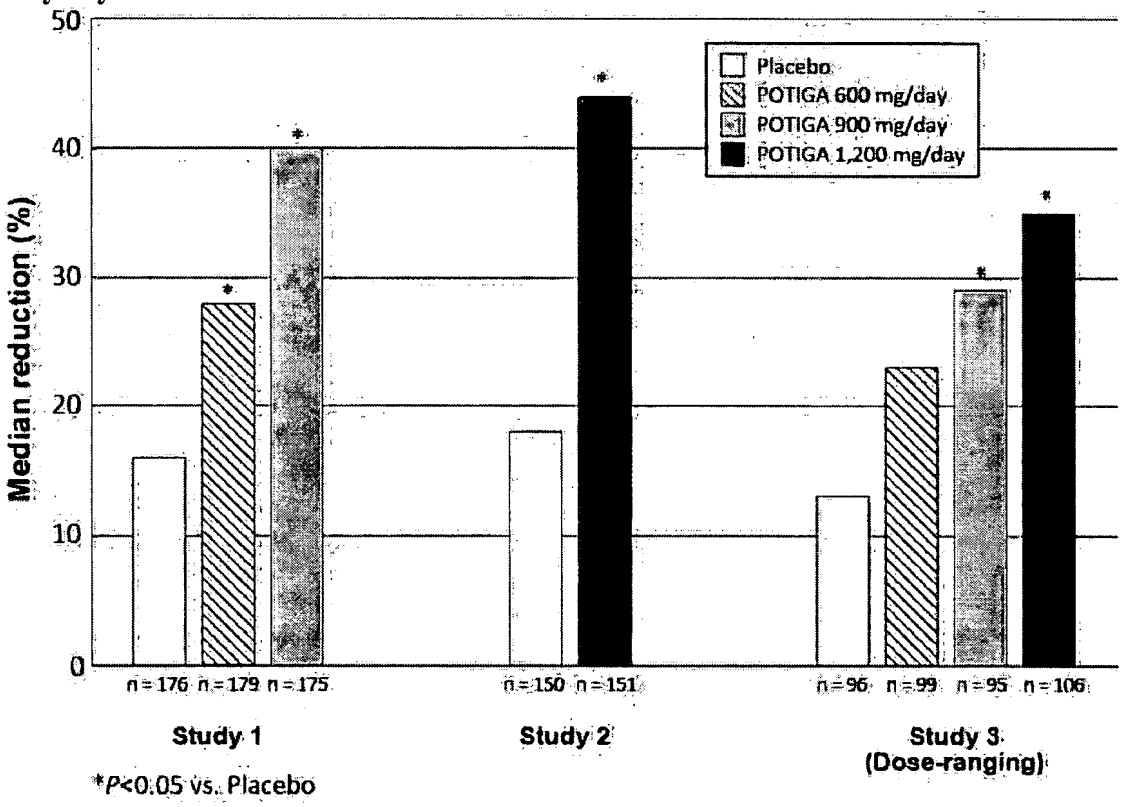
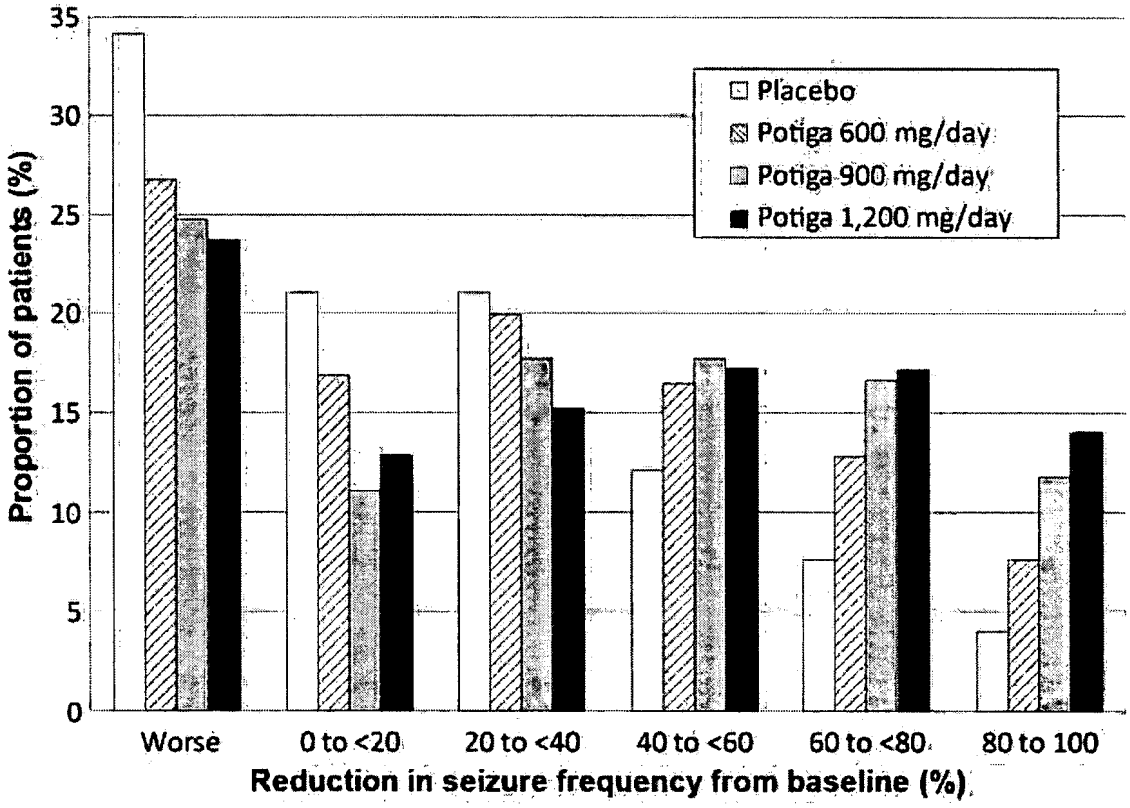



Figure 2 shows changes from baseline in the 28-day total partial seizure frequency by category for patients treated with POTIGA and placebo in an integrated analysis across the 3 clinical trials. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in five categories.

**Figure 2. Proportion of Patients by Category of Seizure Response for POTIGA and Placebo Across All Three Double-blind Trials**




## 16 HOW SUPPLIED/STORAGE AND HANDLING

POTIGA is supplied as film-coated immediate-release tablets for oral administration containing 50, 200, 300, or 400 mg of ezogabine in the following packs:

**50-mg Tablets:** purple, round, film-coated tablets debossed with "RTG 50" on one side in bottles of 90 (NDC 0173-0810-59).

**200-mg Tablets:** yellow, oblong, film-coated tablets debossed with "RTG-200" on one side in bottles of 90 (NDC 0173-0812-59).

**300-mg Tablets:** green, oblong, film-coated tablets debossed with "RTG-300" on one side in bottles of 90 (NDC 0173-0813-59).

**400-mg Tablets:** purple, oblong, film-coated tablets debossed with "RTG-400" on one side in bottles of 90 (NDC 0173-0814-59).

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature.]

## 17 PATIENT COUNSELING INFORMATION

*See FDA-approved patient labeling (Medication Guide).*

### 17.1 Urinary Retention

Patients should be informed that POTIGA can cause urinary retention (including urinary hesitation and dysuria). If patients experience any symptoms of urinary retention, inability to urinate, and/or pain with urination, they should be instructed to seek immediate medical assistance *[see Warnings and Precautions (5.1)]*. For patients who cannot reliably report symptoms of urinary retention (for example, patients with cognitive impairment), urologic consultation may be helpful.

### 17.2 Psychiatric Symptoms

Patients should be informed that POTIGA can cause psychiatric symptoms such as confusional state, disorientation, hallucinations, and other symptoms of psychosis. Patients and their caregivers should be instructed to notify their physicians if they experience psychotic symptoms *[see Warnings and Precautions (5.2)]*.

### 17.3 Central Nervous System Effects

Patients should be informed that POTIGA may cause dizziness, somnolence, memory impairment, abnormal coordination/balance, disturbance in attention, and ophthalmological effects such as diplopia or blurred vision. Patients taking POTIGA should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with POTIGA *[see Warnings and Precautions (5.3)]*.

### 17.4 Suicidal Thinking and Behavior

Patients, their caregivers, and families should be informed that AEDs, including POTIGA, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers *[see Warnings and Precautions (5.5)]*.

### 17.5 Pregnancy

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry collects information about the safety of AEDs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 *[see Use in Specific Populations (8.1)]*.

POTIGA is a trademark of Valeant Pharmaceuticals North America.

Manufactured by Catalent Pharma Solutions
Somerset, NJ 08873

Distributed by



GlaxoSmithKline
Research Triangle Park, NC 27709



June 2011
PTG:1PI

**MEDICATION GUIDE**
**POTIGA™ (po-TEE-ga)**
**(ezogabine)**
**Tablets**

Read this Medication Guide before you start taking POTIGA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have questions about POTIGA, ask your healthcare provider or pharmacist.

**What is the most important information I should know about POTIGA?**
Do not stop POTIGA without first talking to a healthcare provider. Stopping POTIGA suddenly can cause serious problems. Stopping POTIGA suddenly can cause you to have more seizures more often.

1. **POTIGA can make it hard for you to urinate** (empty your bladder) and may cause you to be unable to urinate. Call your healthcare provider right away if you:
   - are unable to start urinating
   - have trouble emptying your bladder
   - have a weak urine stream
   - have pain with urination
2. **POTIGA can cause mental (psychiatric) problems, including:**
   - confusion
   - new or worse aggressive behavior, hostility, anger, or irritability
   - new or worse psychosis (hearing or seeing things that are not real
   - being suspicious or distrustful (believing things that are not true)
   - other unusual or extreme changes in behavior or mood

Tell your healthcare provider right away if you have any new or worsening mental problems while using POTIGA.

3. **Like other antiepileptic drugs, POTIGA may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

   **Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:**
   - thoughts about suicide or dying
   - attempt to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

   Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

**How can I watch for early symptoms of suicidal thoughts and actions?**
- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

**Do not stop POTIGA without first talking to a healthcare provider.**
Stopping POTIGA suddenly can cause serious problems. Stopping POTIGA suddenly can cause you to have more seizures more often.

**What is POTIGA?**
POTIGA is a prescription medicine that is used with other medicines to treat partial onset seizures in people with epilepsy who are 18 years of age or older.

POTIGA can be abused or lead to drug dependence. Keep your POTIGA in a safe place to protect it from theft. Never give your POTIGA to anyone else because it may harm them. Selling or giving away this medicine is against the law.

It is not known if POTIGA is safe and effective in children under 18 years of age.

**What should I tell my healthcare provider before taking POTIGA?**
**Before you take POTIGA, tell your healthcare provider if you:**

- have trouble urinating
- have an enlarged prostate
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have heart problems, including a condition called long QT Syndrome, or have low potassium or magnesium in your blood
- have liver problems
- have kidney problems
- drink alcohol
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if POTIGA will harm your unborn baby.
    - If you become pregnant while taking POTIGA, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. The purpose of this registry is to collect information about the safety of medicines used to treat seizures during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
- are breastfeeding or plan to breastfeed. It is not known if POTIGA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take POTIGA. You and your healthcare provider should decide if you will take POTIGA or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take,** including prescription and non-prescription medicines, vitamins, and herbal supplements. Taking POTIGA with certain other medicines can affect each other, causing side effects. **Especially tell your healthcare provider if you take:**

- digoxin (LANOXIN®, LANOXICAPS®)
- phenytoin (DILANTIN®, PHENYTEK®)
- carbamazepine (CARBATROL®, TEGRETOL®, TEGRETOL®-XR, EQUETRO®, EPITOL®)

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

- Take POTIGA exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much POTIGA to take and when to take it.
- Your healthcare provider may change your dose of POTIGA. Do not change your dose without talking to your healthcare provider.
- POTIGA can be taken with or without food.

- Swallow POTIGA Tablets whole. Do not break, crush, dissolve, or chew POTIGA tablets before swallowing.
- Talk to your doctor about what to do if you miss one or more doses of POTIGA.
- If you take too much POTIGA, call your local Poison Control Center or go to the nearest hospital emergency room right away.

**What should I avoid while taking POTIGA?**

Do not drive, operate machinery, or do other dangerous activities until you know how POTIGA affects you. POTIGA can cause dizziness, sleepiness, double-vision, and blurred vision.

**What are the possible side effects of POTIGA?**

**POTIGA may cause serious side effects, including:**

- See "What is the most important information I should know about POTIGA?"
  **Dizziness and sleepiness.** These symptoms can increase when your dose of POTIGA is increased. See "What should I avoid while taking POTIGA?"
  **Changes in your heart rhythm and the electrical activity of your heart.** Your healthcare provider should monitor your heart during treatment if you have a certain type of heart disease or take certain medications.
- Drinking alcohol during treatment with POTIGA may increase the side effects that you get with POTIGA.

The most common side effects of POTIGA include:

- dizziness
- somnolence
- sleepiness
- tiredness
- confusion
- spinning sensation (vertigo)
- tremor
- problems with balance and muscle coordination, including trouble with walking and moving
- blurred or double vision
- trouble concentrating
- memory problems
- weakness

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of POTIGA. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store POTIGA?**

- Store POTIGA at room temperature at 59°F to 86°F (15°C to 30°C).
- **Keep POTIGA and all medicines out of the reach of children.**

**General information about the safe and effective use of POTIGA.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use POTIGA for a condition for which it was not prescribed. Do not give POTIGA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about POTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about POTIGA that is written for healthcare professionals.

For more information, go to www.potiga.com or call 1-888-825-5249.

**What are the ingredients in POTIGA?**

Active ingredient: ezogabine.
Inactive ingredients in all strengths: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.
50-mg and 400-mg tablets also contain: carmine.
50-mg, 300-mg, and 400-mg tablets also contain: FD&C Blue No 2.
200-mg and 300-mg tablets also contain: iron oxide yellow.

POTIGA is a trademark of Valeant Pharmaceuticals North America.

The brands listed are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its products.

Manufactured by
Catalent Pharma Solutions
Somerset, NJ 08873

Distributed by

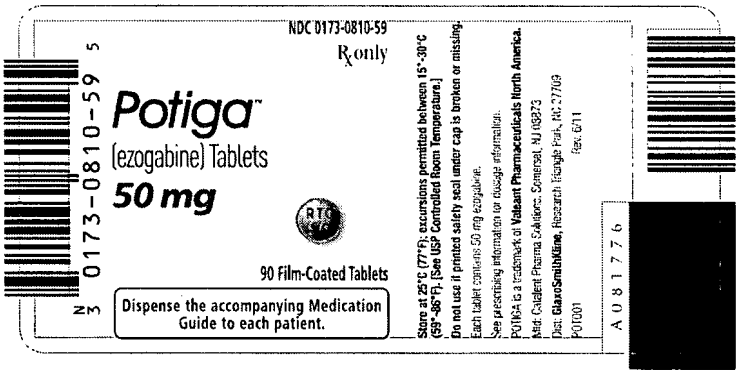


GlaxoSmithKline
Research Triangle Park, NC 27709

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**



June 2011
PTG:1MG




**IMPORTANT**

**GSK Market is responsible for this product, its design and content.**
**Ensure the artwork is thoroughly checked, all the text proof-read and approved.**

**RSC GSK is responsible for site technical requirements and pre-press suitability.**

**GSK Market is responsible to advise RSC in case changes required impact the followings:**

**Formulation, Tablet embossing, Storage conditions, Shelf Life**



| | | |
|---|---|---|
| **GlaxoSmithKline**<br>**Artwork Information Panel** | **Market Trade Name:**<br>Potiga | **No. of Colours:** 4<br>(does NOT include Varnish, if applicable) |
| **Item Number:**<br>10000000081776 | **List Colours:**<br>(include sample in fields provided; e.g. spot / spot-CMYK equivalent) | K C M<br>Varnish 511 |
| **Manufacturing Site:**<br>GSK-USA-Zebulon-USZEB | | |
| **Market or Pack Owner:**<br>United States-USA | **Technical Reference No(s).:**<br>0003021 TS-000370<br>(do NOT include the technical reference doc[s] version no[s].) | **RSC A/W Version:** 3 |

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022345

**NDA APPROVAL**

Valeant Pharmaceuticals North America
Attention: Charity Abelardo, RAC
280 S. Mangum Street, Suite 210
Durham, NC 27701

Dear Ms. Abelardo:

Please refer to your New Drug Application (NDA) dated October 30, 2009, received October 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Potiga (ezogabine) Tablets, 50mg, 200mg, 300mg, and 400 mg.

We acknowledge receipt of your amendments dated April 15 and 21, and June 10, 2011.

The April 15, 2011, submission constituted a complete response to our November 30, 2010, action letter.

This new drug application provides for the use of Potiga as adjunctive treatment for adult patients with partial-onset seizures with or without secondary generalization.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you that on June 21, 2010, you agreed not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when finalized, appropriate revisions will be made to the package insert, the Medication Guide and the container and carton labels through supplementation of your NDA. This would include the statements detailing the scheduling of Potiga in the labeling, as required under 21 CFR 201.57(c)(10)(i).

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for

industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

## CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and the carton and immediate container labels submitted on June 10, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022345**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages zero to 4 weeks of age because the necessary studies are impossible or highly impracticable. This is because there are too few children with this condition to study.

We are deferring submission of your pediatric studies for ages one month to 11 years of age because pediatric studies should be delayed until additional safety and effectiveness data have been collected in an older pediatric age group (12 to 16 years old). We are deferring submission of your pediatric studies for ages 12 to 16 years of age because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1781-1 Conduct a prospective, randomized, placebo-control, double-blinded efficacy/safety trial of Potiga (ezogabine) in children ≥12 years old.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 11/2012 |
| Trial Completion: | 01/2018 |
| Final Report Submission: | 05/2018 |

1781-2 Conduct a long-term open label extension study of ezogabine in children ≥12 years old.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 08/2011 |
| Study Completion: | 07/2019 |
| Final Report Submission: | 11/2019 |

Reports of these required pediatric postmarketing studies must be submitted as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of urinary retention; to identify an unexpected serious risk of drug interactions between ezogabine and drugs that inhibit or induce transporters in the kidney if ezogabine is a substrate for the transporters; to identify an unexpected serious risk of the potential for drug interactions due to inhibition of CYP2B6 by ezogabine when available data indicate the potential for a serious risk; or to identify an unexpected serious risk of the potential for chronic administration of ezogabine to produce a withdrawal syndrome following drug discontinuation.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1781-3 A prospective cohort study to better define the risk of urinary retention in patients with epilepsy treated with ezogabine and how the risk may vary with demographics (e.g. age), comorbidities that influence voiding (e.g., benign prostatic hyperplasia [BPH], multiple sclerosis) and concomitant medications that may influence voiding. The study will be performed utilizing a research database to compare patients started in two cohorts, those started on ezogabine with those started on other anticonvulsants, for the incidence of urinary retention. The study will analyze approximately 2,000 to 4,000 ezogabine-exposed patients.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 05/2012 |
| Study Completion: | 09/2014 |
| Final Report Submission: | 11/2014 |

1781-4 An *in vitro* study to evaluate whether ezogabine is a substrate for major transporters in the kidney. Refer to the Agency's Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf) for more detailed recommendations regarding transporter-based drug-drug interactions.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 09/2011 |
| Study Completion: | 10/2011 |
| Final Report Submission: | 11/2011 |

1781-5 An *in vitro* study to evaluate the potential for ezogabine to inhibit CYP2B6.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 09/2011 |
| Study Completion: | 10/2011 |
| Final Report Submission: | 11/2011 |

1781-6 An animal physical dependence study to evaluate whether chronic administration of ezogabine produces a withdrawal syndrome following drug discontinuation. Refer to the "Guidance for Industry: Assessment of Abuse Potential of Drugs" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf for information about how to design abuse-related studies, including a physical dependence study.

The timetable you submitted on June 6. 2011, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 11/2011 |
| Study Completion: | 01/2012 |
| Final Report Submission: | 05/2012 |

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the mechanism for a known serious risk of urinary retention or to identify an unexpected serious risk for drug interaction with P-glycoprotein substrates when available data indicate the potential for a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1781-7 A controlled urodynamic trial, to include adults of both sexes in a wide range of ages, including the elderly. Pre- and post-drug urodynamic measures should be carefully collected. Urodynamic measurements should include, although not necessarily be limited to, uroflowmetry, multichannel cystometry, electromyography (EMG), and subjective sensory reporting.

The timetable you submitted on June 2, 2011, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 01/2012 |
| Study Completion: | 07/2015 |
| Final Report Submission: | 11/2015 |

1781-8 A clinical trial to evaluate the acetyl metabolite of ezogabine (NAMR) as an inhibitor of P-glycoprotein using digoxin as a probe substrate. Refer to the Agency's Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf) for more detailed recommendations regarding transporter-based drug-drug interactions.

| | |
|---|---|
| Final Protocol Submission: | 11/2011 |
| Trial Completion: | 04/2012 |
| Final Report Submission: | 08/2012 |

Submit the draft protocols approximately 45 days in advance of the final protocol submission dates to allow for Agency review and comment.

Submit the protocols and amendments to your IND 053950 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as

appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letters dated August 16, 2010 and May 25, 2011.

Your proposed REMS, submitted on June 9, 2011, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

a. An evaluation of prescribers' and pharmacists' understanding of the serious risks of Potiga (ezogabine)
b. Date of retail availability of Potiga
c. Sources of lists of prescriber and pharmacist addresses
d. Date(s) of distribution
e. Method of distribution (e.g., mail, email, contract carrier, etc.)
f. Number of recipients on each distribution list

g. Number of documents returned (undelivered)
h. List of all documents included in each distribution
i. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If you plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022345 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 022345**
**PROPOSED REMS MODIFICATION**
**REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 022345**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

## POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Stephanie Keefe, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS
REMS Materials

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ELLIS F UNGER
06/10/2011

Commissioner for Patents
United States Patent and Trademark Office
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Customer No 909 | ISTMT | DATE PRINTED 07/26/2011

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P.O. BOX 10500
MCLEAN VA 22102

# MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

| PATENT NUMBER | FEE AMT | SUR CHARGE | PYMT DATE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| **6,538,151** | **$900.00** | **$0.00** | **09/01/06** | **09/181,671** | **03/25/03** | **10/29/98** | **04** | **NO** | **081117-0125** |

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

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# MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

| PATENT NUMBER | FEE AMT | SUR CHARGE | PYMT DATE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| **6,538,151** | **$2,480.00** | **$0.00** | **09/27/10** | **09/181,671** | **03/25/03** | **10/29/98** | **08** | **NO** | **MWESD 081117-20722 (3592)** |

# 2. DRUG SUBSTANCE SALT AND CRYSTALLINE FORMS

Retigabine was initially synthesized as its dihydrochloride salt and early nonclinical development work was initiated with the salt. Due to instability and purification issues, a decision was made to develop retigabine free-base, which was readily crystallized with high purity and was more stable in comparison to the dihydrochloride.

Retigabine free-base shows crystallographic polymorphism. Five anhydrous/non-solvated crystalline forms of retigabine (Forms A, B, C, E and F) have been discovered to date. A formamide solvate (Form D) was also discovered during form screening but is not relevant to the primary or secondary process as formamide is not used in either process. Refer to Section 3.2.S.1.3, for polymorphism details on the free-base.

All significant nonclinical, clinical, and formulation studies have been carried out with solid-state Form A of retigabine free-base.

Each of the known forms can be differentiated using X-ray powder diffraction and IR spectroscopy, Section 3.2.S.1.3.

Control of solid-state form is described in Section.5.1.

# Retigabine FDA Submission Log for Epilepsy
## IND 53,950



| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 2 | 1997-06-16 | N/A | Pre-IND Meeting Request | Paul Leber, MD |
| 3 | 1997-08-14 | 000 | Original NDA (19 Volumes) | Paul Leber, MD |
| 4 | 1997-08-26 | 000-FDA | FDA Acknowledge receipt of IND and No. issuance 53,950 | John Purvis |
| 5 | 1997-09-24 | Tcon-FDA | T-Con with FDA: (Project Mgr, Division of Neuropharmacological Drug Prod.) 1. Determination if Segment 3 studies are needed to support a short-termclinical trial in children; 2. Follow up on discussionof Sept 17 regarding the acceptability of the proposed toxicoloby development plan to support long term trials in children and adults. | Malina Malandruco |
| 6 | 1997-10-03 | Ltr-FDA | FDA Letter no objection to the Initialtion of clinical studies but with requests and comments. | Paul Leber, MD |
| 7 | 1997-10-07 | 000-FDA | FDA response - Requests and comments to IND submission (Faxed to Wyeth/R. Baranello on Oct 9, 1997) | Paul Leber, MD |
| 8 | 1997-10-31 | 001 | Information Amendment / PharmTox (Report No 29970, 29995, 29996, 30052, 30119, 30168, 30872, 31050-52) (4 Volumes) | Paul Leber, MD |
| 9 | 1997-11-03 | 000-FDA | FDA Telephone Contact - Discussed GKE-841 - NMDA Receptor Antagonist (K. Bonk) | Melina Malandrucco |
| 10 | 1997-11-03 | 000-FDA | Fax to Ken Bonk - Correction to Oct 7, 1997 letter | Melina Malandrucco |
| 11 | 1997-11-20 | 002 | General Correspondence: Response to FDA Letters dated Oct 7, 1997 and Nov 3, 1997 | Paul Leber, MD |
| 12 | 1997-12-05 | 000-FDA | FDA Telephone Contact - Discussed GKE-841 - NMDA Receptor Antagonis and Pediatric Trials (K. Bonk) | Melina Malandrucco |
| 13 | 1998-01-12 | 002-FDA | FDA Telephone Contact - Discussed NMDA Receptor Antagonist and Pediatric Trials (K. Bonk) | Melina Malandrucco |
| 14 | 1998-01-05 | 003 | Protocol Amendment #1: Change in Protocol (3065A1-102-US) | Paul Leber, MD |

# Retigabine FDA Submission Log for Epilepsy
## IND 53,950

| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 15 | 1998-01-26 | 004 | Information Amendment / PharmTox (Report No 30411, 30412, 32010) (2 Volumes w/n 1 Binder) | Paul Leber, MD |
| 16 | 1998-01-28 | 005 | Protocol Amendment: New Protocol (3065A1-202-US) | Paul Leber, MD |
| 17 | 1998-02-24 | 006 | Protocol Amendment #2: Change in Protocol (3065A1-102-US) | Paul Leber, MD |
| 18 | 1998-03-05 | 007 | Information Amendment / CMC (Sec 7.2, 7.3, 7.5) | Paul Leber, MD |
| 19 | 1998-03-20 | 008 | Protocol Amendment: New Investigators (3065A1-202-US) | Paul Leber, MD |
| 20 | 1998-04-01 | 009 | Information Amendment / PharmTox (Report No 32869) | Paul Leber, MD |
| 21 | 1998-04-13 | 010 | Information Amendment / PharmTox (Report No 30973, 32491, 32510) | Paul Leber, MD |
| 22 | 1998-04-21 | 011 | Protocol Amendment #1: Change in Protocol (3065A1-202-US) | Paul Leber, MD |
| 23 | 1998-05-21 | 012 | Protocol Amendment: New Protocol (3065A1-107-US) | Paul Leber, MD |
| 24 | 1998-06-10 | 013 | Protocol Amendment: New Protocol (3065A1-208-US) | Paul Leber, MD |
| 25 | 1998-07-22 | 014 | Request for FDA Feedback: Preclinical Study Protocols for Support of Pediatric Clinical Trials | Paul Leber, MD |
| 26 | 1998-08-28 | 014-FDA | FDA Telephone Contact - Discussed GKE-841 - Preclinical study Protocols for pediatric clinical trials (K. Bonk) | Melina Malandrucco |
| 27 | 1998-09-11 | 014-FDA | FDA Telephone Contact - Discussed GKE-841 - Preclinical study Protocols for pediatric clinical trials (K. Bonk) | Melina Malandrucco |
| 28 | 1998-09-18 | 014-FDA | FDA Telephone Contact - Discussed GKE-841 - Preclinical study protocols for pediatric clinical trials (K. Bonk) | Melina Malandrucco |
| 29 | 1998-09-21 | 014-FDA | FDA response to Ser 14 (GKE-41 pediatric Protocols) | Paul Leber, MD |
| 30 | 1998-07-29 | 015 | IND Safety Report: Initial (3065A1-107-US; Pat #10705006) | Paul Leber, MD |

# Retigabine FDA Submission Log for Epilepsy
# IND 53,950

| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 31 | 1998-08-14 | 016 | Information Amendment / PharmTox (Report No 31053, 33496, 33578) | Paul Leber, MD |
| 32 | 1998-08-28 | 017 | Protocol Amendment: Deletion of Subinvestigator (3065A1-202-US) | Paul Leber, MD |
| 33 | 1998-09-03 | 018 | Protocol Amendment: New Protocol (3065A1-109-US) | Paul Leber, MD |
| 34 | 1998-09-10 | 019 | Protocol Amendment #2: Change in Protocol (3065A1-202-US) | Paul Leber, MD |
| 35 | 1998-09-18 | 020 | IND Safety Report: Initial (3065A1-202-US; Pat # 20210015) | Paul Leber, MD |
| 36 | 1998-09-24 | 021 | Protocol Amendment: Addition of Subinvestigators (3065A1-202-US) | Paul Leber, MD |
| 37 | 1998-09-25 | 022 | IND Safety Report: Follow-up (3065A1-202-US - Ser No. 20) | Paul Leber, MD |
| 38 | 1998-10-09 | 023 | Protocol Amendment #1: Change in Protocol (3065A1-208-US) | Paul Leber, MD |
| 39 | 1998-10-14 | 024 | Information Amendment / CMC (Sec 7.1, 7.2, 7.3, 7.5) | Paul Leber, MD |
| 40 | 1998-10-15 | 025 | Protocol Amendment: New Protocol (3065A1-108-US) | Paul Leber, MD |
| 41 | 1998-10-20 | 026 | Annual Report (GKE-841) | Paul Leber, MD |
| 42 | 1998-10-21 | 027 | Protocol Amendment: Addition of Subinvestigator (3065A1-202-US) | Paul Leber, MD |
| 43 | 1998-10-21 | 028 | IND Safety Report: Follow-up (3065A1-202-US - Ser No. 20) | Paul Leber, MD |
| 44 | 1998-10-22 | 029 | Protocol Amendment: Addition of Subinvestigator (3065A1-208-US) | Paul Leber, MD |
| 45 | 1998-10-23 | 030-FDA | FDA Telephone Contact - Dose levels in long-term, open-label clinical study (3065A1-208-US) (Filed in LL under SN030 Response to FDA) | Drs. Russell Katz, Melina Malandrucco, Joel Freiman, Ed Fisher |
| 46 | 1998-10-30 | 030 | FAX: Response to FDA Request for Info: Protocol 3065A1-208-US (Ref to FDA telephone contact on 10-23-98 and Ser No 23) | Paul Leber, MD |

# Retigabine FDA Submission Log for Epilepsy
## IND 53,950

| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 47 | 1998-10-30 | 030-FDA | T-Con Dose levels in long term, open label clinical study (3065A1-208-US) (Filed in LL under SN030 Response to FDA) | Melina Malandrucco |
| 48 | 1998-11-03 | 030-FDA | T-Con Dose levels in long term, open label clinical study (3065A1-208-US) (Filed in LL under SN030 Response to FDA) | Melina Malandrucco |
| 49 | 1998-11-04 | 013-FDA | T-Con Cancellation to FDA teleconference for today (11/4/98) (Filed in LL under SN030 Response to FDA) Protocol 3065A1-208-US | Melina Malandrucco |
| 50 | 1998-11-10 | 013-FDA | FDA Telephone Contact - Follow-up to Oct 23, 1998 call - Dose levels in long-term, open-label clinical study (3065A1-208-US) (Filed in LL under SN030 Response to FDA) | Russell Katz, Melina Malandrucco, Joel Freiman, Glenna Fitzgerald, Ed Fisher |
| 51 | 1998-11-17 | 030-FDA | T-Con Comparative Oral Bioavailability Study (110-US) Study 108 US C Study (Filed in LL under SN030 Response to FDA) | Melina Malandrucco |
| 52 | 1998-11-17 | 030-FDA | Fax to FDA as requested in T-con for 12 pages including table of contents and Protocol synopsis (3065A1-110-US) (Filed under SN-037) | Melina Malandrucco |
| 53 | 1998-11-20 | 025-FDA | T-Con Comparative Oral Bioavailablity Study (110)-US Study-108-US C Study. Dr. Freiman, reviewed the provided protocol synopsis for study 110-US and agreed that the study can proceed. | Melina Malandrucco |
| 54 | 1998-11-04 | 31 | IND Safety Report: Follow-up (3065A1-202-US - Ser No. 20) | Paul Leber, MD |
| 55 | 1998-11-06 | 32 | IND Safety Report: Initial (3065A1-200-EU, Pat #8001538) | Paul Leber, MD |
| 56 | 1998-11-09 | 33 | IND Safety Report: Initial (3065A1-200-EU, Pat #8001544) | Paul Leber, MD |
| 57 | 1998-11-12 | 34 | IND Safety Report: Initial (3065A1-208-US, Pat #20878003) | Paul Leber, MD |
| 58 | 1998-11-19 | 35 | Protocol Amendment: Addition of Subinvestigator (3065A1-208-US) | Paul Leber, MD |

# Retigabine FDA Submission Log for Epilepsy
## IND 53,950

| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 59 | 1998-11-20 | 36 | Information Amendment / CMC (Sec 7.2, 7.3, 7.5) | Paul Leber, MD |
| 60 | 1998-11-23 | 37 | Protocol Amendment: New Protocol (3065A1-110-US) | Paul Leber, MD |
| 61 | 1998-12-08 | 38 | Safety Report: Follow-up (3065A1-202-US - Ser No. 20) | Paul Leber, MD |
| 62 | 1998-12-15 | 39 | Information Amendment / PharmTox (Report No 32826) | Paul Leber, MD |
| 63 | 1998-12-17 | 40 | Protocol Amendment #3: Change in Protocol (3065A1-202-US) | Paul Leber, MD |
| 64 | 1998-12-18 | 41 | Protocol Amendment #2: Change in Protocol (3065A1-208-US) | Paul Leber, MD |
| 65 | 1999-02-23 | 42 | Information Amendment / PharmTox (Report No 30897, 34502) | Russell Katz, MD |
| 66 | 1999-03-03 | 43 | Protocol Amendment: Addition of Subinvestigator (3065A1-109-US) | Russell Katz, MD |
| 67 | 1999-03-26 | 44 | Information Amendment / PharmTox (Report No 33381) | Russell Katz, MD |
| 68 | 1999-04-08 | 45 | Information Amendment / PharmTox (Report No 36746) | Russell Katz, MD |
| 69 | 1999-04-20 | 46 | Response to FDA Request for Info: Protocol 3065A1-208-US (Ref to FDA telephone contact on 11-9-98, Ser No 23 & 30) | Russell Katz, MD |
| 70 | 1999-04-29 | 47 | General Correspondence: Draft Protocol (3065A1-205-EU) for FDA Concurrence (Ref to FDA telephone contact on 10-23-98 and 11-9-98) | Russell Katz, MD |
| 71 | 1999-05-11 | 47-FDA | FDA Telephone Contact - FDA concurrence on Initiation of Study 205 | Melina Malandrucco |
| 72 | 1999-05-28 | 47-FDA | FDA Response fax to draft protocol 3065A1-205-EU | Melina Malandrucco |
| 73 | 1999-06-01 | 47-FDA | FDA Telephone Contact on 5-20, 5-26 and 5-28 - Follow-up to Ser 47 regarding FDA concurrence | Melina Malandrucco |
| 74 | 1999-05-12 | 48 | Information Amendment / PharmTox (Report No 34218, 34247) (2 binders) | Russell Katz, MD |

# Retigabine FDA Submission Log for Epilepsy
## IND 53,950

| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 75 | 1999-05-13 | 49 | Protocol Amendment #3: Change in Protocol (3065A1-208-US) | Russell Katz, MD |
| 76 | 1999-05-20 | 50 | Information Amendment / PharmTox (Report No 36674, 36678, 36706) (2 binders) | Russell Katz, MD |
| 77 | 1999-06-01 | 047-FDA | T-Con with FDA re: Concurrence on Initiation of Study 205 | Melina Malandrucco |
| 78 | 1999-06-02 | 51 | Protocol Amendment: Addition of Subinvestigator (3065A1-208-US) | Russell Katz, MD |
| 79 | 1999-06-03 | 52 | Protocol Amendment: Addition of Subinvestigator (3065A1-202-US) | Russell Katz, MD |
| 80 | 1999-06-07 | 53 | Information Amendment / PharmTox (Report No 33896, 33897) | Russell Katz, MD |
| 81 | 1999-06-24 | Tcon-FDA | T-Con with FDA: Need for a Separate IND for Pediatric Formulation | Melina Maladrucco |
| 82 | 1999-07-21 | 54 | Information Amendment / PharmTox (Report No 30044) | Russell Katz, MD |
| 83 | 1999-08-09 | 55 | Information Amendment / PharmTox (Report No 37683) | Russell Katz, MD |
| 84 | 1999-08-25 | 56 | Information Amendment / PharmTox (Report No 35111, 37460, 37687) | Russell Katz, MD |
| 85 | 1999-09-08 | 57 | Information Amendment / PharmTox - Modification of Juvenile Animal Toxicity Study (Ref Ser 14) | Russell Katz, MD |
| 86 | 1999-09-13 | 58 | Information Amendment / PharmTox (Report No 33496, 33578, 34343, 34694, 35109) | Russell Katz, MD |
| 87 | 1999-09-23 | 59 | IND Safety Report: Follow-up (3065A1-208-US - Ser No 34) | Russell Katz, MD |
| 88 | 1999-10-07 | 60 | IND Safety Report: Follow-up (3065A1-208-US - Ser No 34) | Russell Katz, MD |
| 89 | 1999-10-11 | 61 | General Correspondence: Response to FDA Letter dated Oct 7, 1997 (Genotoxicity) | Russell Katz, MD |
| 90 | 1999-10-13 | 62 | IND Safety Report: Follow-up (3065A1-107-US - Ser No 15) | Russell Katz, MD |
| 91 | 1999-10-27 | 63 | Protocol Amendment #4: Change in Protocol (3065A1-208-US) | Russell Katz, MD |

# Retigabine FDA Submission Log for Epilepsy
## IND 53,950

| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 92 | 1999-10-28 | 64 | Protocol Amendment: Addition of Subinvestigator and Information Amendment: Clinical (3065A1-202-US & 3065A1-208-US) | Russell Katz, MD |
| 93 | 1999-11-03 | 65 | Information Amendment / PharmTox (Report No 34789, 34798, 34799, 37328, 37574) | Russell Katz, MD |
| 94 | 1999-11-04 | 66 | Information Amendment / CMC (Sec 7.3, 7.4, 7.5) | Russell Katz, MD |
| 95 | 1999-12-16 | 67 | Request for FDA Feedback: Clarification of Preclinical Pediatric Clinical Trials | Russell Katz, MD |
| 96 | 1999-12-22 | 68 | Protocol Amendment: New Protocol (3065A1-112-US) | Russell Katz, MD |
| 97 | 1999-12-28 | 69 | Information Amendment / PharmTox (Report No 36451, 36452) | Russell Katz, MD |
| 98 | 2000-01-12 | 61-FDA 67-FDA | FDA Telephone Contact dated 12-28-99, 1-4-00, 1-11-00, 1-12-00 - FDA concurrence on lack of RGB mutagenicity liability and delineation of pediatric clinical trials (Ref Ser No 61 and 67) | Melina Malandrucco |
| 99 | 2000-01-13 | 67-FDA | FDA Letter regarding SN 067 | Russell Katz, MD |
| 100 | 2000-02-14 | 61-FDA | FDA Telephone Contact dated 2-11-00, 2-14-00 - FDA concurrence on lack of RGB mutagenicity liability (Ref Ser No 61) | Melina Malandrucco |
| 101 | 2000-02-22 | 61-FDA | FDA response letter to Ser No 61 regarding mutagenicity. | Russell Katz, MD |
| 102 | 2000-01-13 | 67-FDA | FDA response letter to Ser No 67 | Russell Katz, MD |
| 103 | 2000-01-19 | 70 | Protocol Amendment #1: Change in Protocol (3065A1-112-US) | Russell Katz, MD |
| 104 | 2000-02-03 | 71 | IND Safety Report: Initial (3065A1-205-EU; Pat # 125) | Russell Katz, MD |
| 105 | 2000-02-04 | 72 | Information Amendment / PharmTox (Report No 36450, 38362) | Russell Katz, MD |
| 106 | 2000-02-08 | 73 | General Correspondence: Response to FDA Request for Cardiac Data (Re: Protocol 3065A1-205-EU; Ser No 47) | Russell Katz, MD |
| 107 | 2000-02-10 | 74 | Protocol Amendment: New Protocol (3065A1-205-US) | Russell Katz, MD |

# Retigabine FDA Submission Log for Epilepsy
# IND 53,950

| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 108 | 2000-03-03 | 75 | Annual Report (GKE-841) | Russell Katz, MD |
| 109 | 2000-03-10 | 76 | Protocol Amendment: New Protocol (3065A1-121-US) | Russell Katz, MD |
| 110 | 2000-03-16 | 77 | IND Safety Report: Initial (3065A1-205-EU, Pat #14) | Russell Katz, MD |
| 111 | 2000-03-27 | 78 | Protocol Amendment #2: Change in Protocol (3065A1-112- | Russell Katz, MD |
| 112 | 2000-04-24 | 79 | Protocol Amendment #1: Change in Protocol (3065A1-121- | Russell Katz, MD |
| 113 | 2000-04-26 | 80 | IND Safety Report: Initial (3065A1-205-EU, Pat #457) | Russell Katz, MD |
| 114 | 2000-05-02 | 81 | IND Safety Report: Follow-up (3065A1-205-EU, Ser No 77) | Russell Katz, MD |
| 115 | 2000-05-05 | 82 | Protocol Amendment #5: Change in Protocol (3065A1-208- | Russell Katz, MD |
| 116 | 2000-05-19 | 83 | IND Safety Report: Initial (3065A1-205-EU, Pat #14) | Russell Katz, MD |
| 117 | 2000-06-01 | 84 | IND Safety Report: Initial (3065A1-209-EU, Pat #10, Control No HQ6216422MAY2000) | Russell Katz, MD |
| 118 | 2000-06-02 | 85 | IND Safety Report: Initial (3065A1-205-EU, Pat #60, Control No. HQ6628331MAY2000) | Russell Katz, MD |
| 119 | 2000-06-02 | 85-FDA | FDA Telephone Contact - Retigabine: 7-day safety report (as reported in Ser No 85) | Robbin Nighswander |
| 120 | 2000-06-19 | 86 | Protocol Amendment: New Investigators (3065A1-205-US) | Russell Katz, MD |
| 121 | 2000-06-19 | 87 | IND Safety Report: Follow-up (3065A1-205-EU - Ser No 85) | Russell Katz, MD |
| 122 | 2000-06-22 | 88 | IND Safety Report: Follow-up (3065A1-205-EU - Ser No 77) | Russell Katz, MD |
| 123 | 2000-07-28 | 89 | Information Amendment / PharmTox (Report No 38025, 38546, 39872, 39876, 39877, 39909) | Russell Katz, MD |
| 124 | 2000-08-02 | 90 | IND Safety Report: Initial (3065A1-208-US, Pat #2, Control No. HQ8844121JUL2000) | Russell Katz, MD |
| 125 | 2000-08-03 | 91 | IND Safety Report: Follow-up (3065A1-205-EU - Ser No 85) | Russell Katz, MD |
| 126 | 2000-08-15 | 92 | Information Amendment / PharmTox (Report No 34425, 34438, 36908, 36915, 37007, 37239, 38261, 38286, 38869,38372) | Russell Katz, MD |
| 127 | 2000-08-17 | 93 | Protocol Amendment #1: Change in Protocol (3065A1-205- | Russell Katz, MD |
| 128 | 2000-08-31 | 94 | Protocol Amendment: New Investigators (3065A1-205-US) | Russell Katz, MD |

# Retigabine FDA Submission Log for Epilepsy
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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 129 | 2000-09-19 | 95 | Protocol Amendment: New Protocol (3065A1-214-US) | Russell Katz, MD |
| 130 | 2000-10-03 | 96 | Information Amendment / PharmTox (Report No 36381, 37574, 39365, 39956, 38871, 38872, 38873, 40124, 35256) | Russell Katz, MD |
| 131 | 2000-10-05 | 97 | IND Safety Report: Follow-up (3065A1-205-EU - Ser No 85) | Russell Katz, MD |
| 132 | 2000-10-25 | 98 | Protocol Amendment: New Protocol (3065A1-212-US) | Russell Katz, MD |
| 133 | 2000-12-06 | 99 | Protocol Amendment #6: Change in Protocol (3065A1-208- | Russell Katz, MD |
| 134 | 2000-12-22 | 100 | Protocol Amendment: New Protocol (3065A1-216-US) | Russell Katz, MD |
| 135 | 2001-01-03 | 101 | IND Safety Report: Follow-up (3065A1-205-EU - Ser No 85) | Russell Katz, MD |
| 136 | 2001-01-03 | 102 | Protocol Amendment: New Investigators (3065A1-214-US) | Russell Katz, MD |
| 137 | 2001-01-03 | 103 | Information Amendment / PharmTox (Report No 39602, 39620, 39881, 41022, 39073, 40811) | Russell Katz, MD |
| 138 | 2001-02-28 | 104 | Protocol Amendment: New Protocol (3065A1-215-US) | Russell Katz, MD |
| 139 | 2001-02-28 | 105 | Annual Report | Russell Katz, MD |
| 140 | 2001-03-26 | 106 | Protocol Amendment: New Investigators (3065A1-212-US) | Russell Katz, MD |
| 141 | 2001-03-29 | 107 | General Correspondence: Dr. Rajesh Sachdeo IND | Russell Katz, MD |
| 142 | 2001-04-19 | 107-FDA | FDA Telephone Contact on 4/19 - cross reference letter for Dr. Sachdeo IND | Melina Fanari |
| 143 | 2001-04-02 | 108 | Request for FDA Feedback: Preclinical Study Protocols for Support of Pediatric Clinical Trials (Ref Ser No 67, Ser No 96 and FDA response on 1/13/01) | Russell Katz, MD |
| 144 | 2001-06-19 | 108-FDA | FDA Telephone Contact on 6/18 and 6/19 - Pediatric Clinical Trials | Melina Fanari |
| 145 | 2001-12-12 | 108-FDA | FDA email corresp. On 12/12 re Pediatric Use (Medical Reviewer Questions | Melina Fanari |
| 146 | 2001-12-12 | 108-FDA | FDA Telephone Contact on 12/12 - Retigabine Pediatric Use - still under FDA review | Melina Fanari |
| 147 | 2001-12-12 | 108-FDA | FDA Email Correspondence on 12/12 - Pediatric Use (Medical Reviewer questions) | Melina Fanari |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 148 | 2001-12-13 | 108-FDA | T Con to provide preliminary responses to Medical Reviewers Requests | Melna Fanari |
| 149 | 2001-12-20 | 108-FDA | FDA Response Letter to Ser No 108 | Russell Katz, MD |
| 150 | 2001-04-09 | 109 | Information Amendment / PharmTox (Report No 41737, 41738, 41824, 41965, 42007, 42145, 42147, 42274, 42295) | Russell Katz, MD |
| 151 | 2001-04-23 | 110 | Protocol Amendment: New Investigators and Addition of SubInvestigator (3065A1-216-US) | Russell Katz, MD |
| 152 | 2001-05-03 | 111 | IND Safety Report: Initial (Preclinical - bacterial reverse mutation assay) | Russell Katz, MD |
| 153 | 2001-05-03 | 112 | IND Safety Report: Initial (Preclinical - 28-day oral toxicity study in dogs) | Russell Katz, MD |
| 154 | 2001-05-21 | 113 | Protocol Amendment #7: Change in Protocol (3065A1-208- | Russell Katz, MD |
| 155 | 2001-05-22 | 114 | Protocol Amendment: New Investigators (3065A1-216-US) | Russell Katz, MD |
| 156 | 2001-05-23 | 115 | IND Safety Report: Initial (3065A1-212-US, Pat #628, Control No. HQ1080121MAY2001) | Russell Katz, MD |
| 157 | 2001-05-31 | 116 | Information Amendment / PharmTox (Report No 41012, 42625, 42745, 35254, 41556, 41920, 42146) | Russell Katz, MD |
| 158 | 2001-06-06 | 117 | IND Safety Report: Follow-up (3065A1-212-EU - Ser No 115) | Russell Katz, MD |
| 159 | 2001-06-19 | Tcon-FDA | T-Con - return call to FDA regarding Pediatric Trials - No ongoing or completed pediatric trials with retigabine. | Ms. Melina Fanari, Project Manager |
| 160 | 2001-06-20 | 118 | Protocol Amendment: Addition/deletion of subinvestigators and Information Amendment: Change of Addresses and IRB (3065A1-205-US) | Russell Katz, MD |
| 161 | 2001-06-20 | 119 | Protocol Amendment: Addition/deletion of subinvestigators and Information Amendment: Change of Addresses and IRB (3065A1-208-US) | Russell Katz, MD |
| 162 | 2001-06-21 | 120 | Protocol Amendment: New Investigator (3065A1-214-US) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 163 | 2001-09-21 | 121 | Protocol Amendment: New Investigator (3065A1-216-US) | Russell Katz, MD |
| 164 | 2001-09-24 | 122 | Information Amendment / PharmTox (Report No 40781, 40782, 41101, 41102, 41105, 42357, 42464, 42745, 43795, 34695, 40756, 40758, 40871, 41237 + 16 more) | Russell Katz, MD |
| 165 | 2001-11-14 | 123 | Protocol Amendment #8: Change in Protocol (3065A1-208-US) | Russell Katz, MD |
| 166 | 2001-11-21 | 124 | Information Amendment / PharmTox (Report No 43416, 43547, 43644, 43691, 43694, 43696, 43760) | Russell Katz, MD |
| 167 | 2001-12-03 | 125 | Protocol Amendment #1: Change in Protocol (3065A1-212-US) | Russell Katz, MD |
| 168 | 2002-01-11 | 126 | Annual Report | Russell Katz, MD |
| 169 | 2002-01-22 | 127 | General Correspondence: Transfer of IND Sponsorship (Wyeth to Asta Medica) | Russell Katz, MD |
| 170 | 2002-02-15 | 128 | IND Safety Report: Initial (Compassionate Use Trial, Pat #126, Control No. HQ0618508FEB2002) and TRANSFER OF OBLIGATIONS | Russell Katz, MD |
| 171 | 2002-02-15 | 128-FDA | FDA T-Con re: who is responsible to submit the initial safety report | Melina Fanari, Sr Project Manager, FDA |
| 172 | 2002-02-18 | 128 | Letter to FDA - Transfer of Obligations from Wyeth to ASTA | Russell Katz, MD |
| 173 | 2002-02-19 | 129 | General Correspondence: Acceptance of IND Sponsorship (Wyeth to ASTA) | Russell Katz, MD |
| 174 | 2002-02-22 | 129-ltr | Letter re: Investigator IND Submission | A.Beydown, U.MI. to H.Kastrup, ASTA |
| 175 | 2002-02-22 | 129-ltr | Letter re: Investigator IND Submission | Abou-Khalil to H.Kastrup, ASTA |
| 176 | 2002-02-25 | 128-FDA, 129-FDA | FDA letter acknowledging change in sponsorship to ASTA Medica (Parexel International) from Wyeth Ayerst Research effective on January 22, 2002. | John S. Purvis, Chief, Project Management Staff |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 177 | 2002-03-07 | 130-ltr | Letter to FDA - Investigator IND Submission | Russell Katz, MD from B.Abou-Khalil |
| 178 | 2002-03-27 | 130 | Letter to FDA - Transfer of Obligations from ASTA to Viatris | Russell Katz, MD |
| 179 | 2002-04-05 | 130-ltr | Letter to FDA - New Investigator IND | Central Doc Room from A.Beydoun, U.MI |
| 180 | 2002-04-09 | 130 | General Correspondence: Sponsor Name Change (Viatris) | Russell Katz, MD |
| 181 | 2002-04-09 | 130-ltr | Notification Letter: Submission of Name Change | G.Glifort, Parexel to E.Schneider, Viatris |
| 182 | 2002-05-23 | 128 SAE | RE: SAE (death) reported in SN128 | G.Glifort, Parexel to E.Bertram-Neis, Viatris |
| 183 | 2002-05-31 | 128 email | RE: Confusion over use of SN128 for reporting both the SAE and transfer of obligations | G.Glifort, Parexel to E.Bertram-Neis, Viatris |
| 184 | 2002-06-28 | 131 | IND Safety Report: Follow-up (Compassionate Use Trial - Ser No 128) | Russell Katz, MD |
| 185 | 2002-09-05 | 132 | General Correspondence: Intent to Submit Carcinogenicity Protocols (Viatris) Protocols 208, 212, 216) | Russell Katz, MD |
| 186 | 2002-09-11 | 133 | General Correspondence: Request for End-of-Phase II (Type B) Meeting (Viatris) | Russell Katz, MD |
| 187 | 2002-09-19 | 134 | Information Amendment / PharmTox (Report No 9321020031, 300899032, 3000922353, 3000922397, 3000922533) | Russell Katz, MD |
| 188 | 2002-10-08 | 135 | Protocol Amendment #4: Change in Protocol (D-23129-3224)<br>Protocol Amendment #2: Change in Protocol (D-23129-3225) | Russell Katz, MD |
| 189 | 2002-10-10 | 136 | General Correspondence: Request for Postponement of End-of-Phase II (Type B) Meeting (Viatris) | Melina Griffis |
| 190 | 2002-10-16 | 137 | General Correspondence: Submission of Carcinogenicity Protocol (Gavage study in rats) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 191 | 2002-10-16 | 138 | General Correspondence: Submission of Carcinogenicity Protocol (Neonatal mice) | Russell Katz, MD |
| 192 | 2002-10-25 | 139 | General Correspondence: Submission of Carcinogenicity Information (Report No 9321020115, 42539) | Russell Katz, MD |
| 193 | 2002-11-14 | 140 | Initial Safety Report: Death (D-23129-3224-US, Pat #126, [20879013NKM]) | Russell Katz, MD |
| 194 | 2002-11-21 | Ltr to FDA | Letter to FDA - Allow Investigator IND for J. McNamara | To FDA Central Doc Rm from H. Kastrup, Viatris |
| 195 | 2002-12-12 | Fax-FDA | FDA Fax communication: Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report. | Adele Seifried HFD-024 |
| 196 | 2002-12-18 | 141 | General Correspondence: Request for End-of-Phase II (Type B) Meeting (Viatris Resubmission) | Russell Katz, MD |
| 197 | 2003-01-22 | 142 | General Correspondence: Response to CAC Meeting Minutes - Request to Reconsider | Russell Katz, MD |
| 198 | 2003-01-24 | 143 | Annual Report<br>Preclinical Information Amendment | Russell Katz, MD |
| 199 | 2003-02-27 | 144 | General Correspondence: Briefing Document for End-of-Phase II Meeting (Scheduled for 3/28/03) | Russell Katz, MD |
| 200 | 2003-03-12 | 145 | General Correspondence: End-of-Phase II Meeting Agenda | Russell Katz, MD |
| 201 | 2003-03-19 | 146 | General Correspondence: End-of-Phase II Meeting Cancellation (Scheduled for 3/28/03) | Russell Katz, MD |
| 202 | 2003-05-19 | 142-FDA | FDA Response re reconsideration of CAC meeting minutes of 22-Jan-2003 | Russell Katz, MD |
| 203 | 2003-12-19 | 147 | Annual Report and Information Amendment / PharmTox for period 01-Oct-2002 to 30-Sep-2003 | Russell Katz, MD |
| 204 | 2003-12-19 | 148 | Information Amendment / Clinical (3065A1-205) (Report No 9352000001) | Russell Katz, MD |
| 205 | 2004-01-04 | 150-ltr | Copy of Transfer Letter | To B.Lu, Xcel from E.Betram-Neis, Viatris |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 206 | 2004-01-14 | 149 | Information Amendment / CMC (Change in capsule color) | Russell Katz, MD |
| 207 | 2004-02-03 | 150 | General Correspondence: Transfer of IND Sponsorship (Viatris to Xcel) | Russell Katz, MD |
| 208 | 2004-02-03 | 151 | General Correspondence: Acceptance of IND Sponsorship (Viatris to Xcel) | Russell Katz, MD |
| 209 | 2004-02-03 | 152 | General Correspondence: Right of Reference to IND | Russell Katz, MD |
| 210 | 2004-04-08 | 153 | General Correspondence: Intent to Submit Carcinogenicity Protocols( Xcel) | Russell Katz, MD |
| 211 | 2004-04-26 | 154 | Information Amendment / PharmTox (Report No 899032 - Asta Medica Study No. 915535) | Russell Katz, MD |
| 212 | 2004-04-28 | 155 | General Correspondence: Request for Special Protocol Assessment (Carcinogenicity Protocol) | Russell Katz, MD |
| 213 | 2004-08-05 | 156 | General Correspondence: Request for End-of-Phase II (Type B) Meeting (Xcel) | Russell Katz, MD |
| 214 | 2004-08-05 | 157 | General Correspondence: Request for End-of-Phase II (CMC) Meeting (Xcel) | Russell Katz, MD |
| 215 | 2004-09-03 | 158 | General Correspondence: End-of-Phase II CMC Meeting Briefing Document (Scheduled for 10/7/04) | Russell Katz, MD |
| 216 | 2004-10-04 | 159 | General Correspondence: 02 November 2004 End-of-Phase II Briefing Document | Russell Katz, MD |
| 217 | 2004-10-07 | 159 | T-Con Minutes of end-of-Phase 2 CMC Meeting between XCEL Pharma and Division of Neuropharmacologic Drug products (HFD-120) | Melina Griffis, FDA |
| 218 | 2004-10-07 | Tcon-FDA | Additional T-Con FDA CMC EOP2 Mtg Min of 10/7/02 | Melina Griffis, FDA |
| 219 | 2004-10-11 | 160 | General Correspondence: Sponsor minutes from agency meeting of 10/07/04 - **End of Phase II CMC Meeting** | Russell Katz, MD |
| 220 | 2004-11-02 | 159FDA | Meeting Minutes - EOP2 CMC between FDA and Sponsor | Melina Griffis, FDA |
| 221 | 2004-12-08 | Min-FDA | General Correspondence: FDA Meeting Minutes of 11/2/2004 (Duplicate of 2004-11-02) | Melina Griffis, FDA |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 222 | 2004-12-13 | 161 | General Correspondence: Sponsor minutes from agency meeting of 11/02/04 | Russell Katz, MD |
| 223 | 2005-01-28 | 162 | Annual Report and Clinical Information Amendment (CSRs for 3065A1 -208-US and -212; and two nonIND studies) | Russell Katz, MD |
| 224 | 2005-05-05 | 163 | General Correspondence: **Transfer of IND Ownership** from Xcel to Valeant Pharmaceuticals North America | Russell Katz, MD |
| 225 | 2005-05-13 | 164 | General Correspondence: Request for SPA (VRX-RET -E22-301) | Russell Katz, MD |
| 226 | 2005-05-13 | 165 | General Correspondence: Request for SPA (VRX-RET -E22-302) | Russell Katz, MD |
| 227 | 2005-06-24 | 166 | Information Amendment / CMC (Film-coated tablets) | Russell Katz, MD |
| 228 | 2005-06-29 | 164-FDA 165-FDA | FDA Comments re SPA 301 & 302 (SN 164 & 165) response to 13-May-2005 Correspondence | Russell Katz, MD |
| 229 | 2005-07-19 | 167 | Information Amendment: CMC (Microcrystalline Cellulose Grades) | Russell Katz. M.D. |
| 230 | 2005-07-21 | 164-FDA 165-FDA | FDA Meeting Minutes re: SPA 301 & 302 (SN 164 & 165) | C. Calder, FDA |
| 231 | 2005-07-27 | 168 | Information Amendment: Clinical (Revised Investigator's Brochure, Edition Number 6, Release Date June 13, 2005) | Russell Katz, M.D. |
| 232 | 2005-08-10 | 169 | General Correspondence: Response to Comments in the Agency's December 12, 2002 "Response to Carcinogenicity Special Protocol Assessment Request – Final CAC Report" | Russell Katz, M.D. |
| 233 | 2005-08-18 | 164-FDA | FDA letter recommending changes to Protocol 301 regarding QTc interval | Russell Katz, M.D. |
| 234 | 2005-09-01 | 170 | Protocol Amendment: Change in Protocol for VRX-RET-E22-301 and VRX-RET-E22-302 Protocols | Russell Katz, M.D. |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 235 | 2005-09-14 | 169-FDA | T-Con Calls and Emails with FDA re: SN 169 on Sep. 12 and 14, 2005 | Courtney Calder - FDA and Rich Heller - Valeant |
| 236 | 2005-10-05 | 171 | Protocol Amendment: New Investigator for 301 Protocol (Site Nos. 002 and 016) | Russell Katz. M.D. |
| 237 | 2005-11-03 | 172 | Protocol Amendment: New Investigator for 301 Protocol (Site Nos.008, 009 and 017) / Revised 1572 for Site No. 002 | Russell Katz, M.D. |
| 238 | 2005-12-02 | 173 | Protocol Amendment: New Investigator for 301 Protocol (Site Nos. 005, 014, 020, and 025) | Russell Katz, M.D. |
| 239 | 2006-01-03 | 174 | Protocol Amendment: New Investigator for 301 Protocol (Site Nos. 004 and 006) | Russell Katz, MD |
| 240 | 2006-01-20 | 175 | Annual Report for October 1, 2004 to September 30, 2005 Period | Russell Katz, MD |
| 241 | 2006-01-23 | 176 | Protocol Amendment: New Investigator for 302 Protocol (Site No. 255) | Russell Katz, MD |
| 242 | 2006-01-26 | 177 | Information Amendment: Pharmacology - Toxicology (Request to Discontinue High Dose of PR2005-080 Study) | Russell Katz, MD |
| 243 | 2006-02-02 | 178 | Protocol Amendment: New Investigator for 301 Protocol (Site Nos. 010, 018, 021, 023, 026; revision for site no. 005; discontinuation for site no. 016) | Russell Katz, MD |
| 244 | 2006-02-13 | 179 | Protocol Amendment: New Protocol for VRX-RET-E22-303 and VRX-RET-E22-304 OLE Studies | Russell Katz, MD |
| 245 | 2006-02-24 | 180 | Protocol Amendment: New Investigator for 302 Protocol (Site Nos. 301, 303, 601, 701, 702, 703, 704) | Russell Katz, MD |
| 246 | 2006-03-06 | 181 | Protocol Amendment: New Investigator for 301 Protocol (Site Nos. 001, 003, 012, 015, 019, 051, 053, 106; revised site nos. 018 and 026) | Rusasell Katz, MD |
| 247 | 2006-03-21 | 182 | Protocol Amendment: New Protocol for VRX-RET-E22-101 (Renal Insufficiency) Study | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 248 | 2006-03-27 | 183 | Protocol Amendment: New Investigator for 302 Protocol (Site Nos. 402, 405, 451, 453, 602, 603, 604, 605, 606, 851, 852, 853, 854) / Site Specific Administrative Change for Site No. 302 | Russell Katz, MD |
| 249 | 2006-04-17 | 184 | Protocol Amendment: Change in Protocol for 301 and 302 Protocols / New Investigator for 301 (Site Nos. 013, 027, 102; revised site nos. 001 and 010) and 302 (Site No. 304) Protocols | Russell Katz, MD |
| 250 | 2006-04-21 | 185 | General Correspondence: Draft QTc Protocol 103 - Request for Comments | Russell Katz, MD |
| 251 | 2006-05-17 | 185-FDA | E-mail with FDA requesting Word version of QTc draft Protocol 103 submitted on April 21,2006 | Courtney Calder - FDA and Rich Heller - Valeant |
| 252 | 2006-05-17 | 186 | Protocol Amendment: New Investigator for Protocols 301, 302, and 303 | Russell Katz, MD |
| 253 | 2006-06-30 | 159-FDA | Email from FDA re Stability requirements for drug substance | Courtney Calder - FDA and Amadeo Fernandez - Valeant |
| 254 | 2006-07-07 | 185-FDA | FDA response to SN185 QTc draft protocol 103 dated April 21, 2006 | Russell Katz, MD |
| 255 | 2006-07-21 | 187 | Protocol Amendment: New Investigator for 301 Protocol (Site Nos. 024, 028, 151, 152, 153, 154, 156, 201, 203; revised site nos. 015 and 051; discontinue site no. 005) | Russell Katz, MD |
| 256 | 2006-07-21 | 188 | Protocol Amendment: New Investigator for 302 Protocol (Site Nos. 252, 401, 553, 651, 652) | Russell Katz, MD |
| 257 | 2006-07-21 | 189 | Protocol Amendment: New Investigator for 303 Protocol (Site Nos. 025, 027) | Russell Katz, MD |
| 258 | 2006-07-25 | 190 | Safety Report 2006VX000843 Initial (Protocol 302) | Russell Katz, MD |
| 259 | 2006-08-02 | 191 | Safety Report 2006VX000843 FU1 (Protocol 302) | Russell Katz, MD |
| 260 | 2006-08-10 | 192 | Safety Report 2006VX000843 FU2 (Protocol 302) | Russell Katz, MD |
| 261 | 2006-08-29 | 193 | Safety Report 2006VX001102 Initial (Protocol 301) | Russell Katz, MD |
| 262 | 2006-09-14 | 194 | Safety Report 2006VX001263 Initial (Protocol 301) | Russell Katz, MD |
| 263 | 2006-09-26 | 195 | Safety Report 2006VX000843 FU3 (Protocol 302) | Russell Katz, MD |
| 264 | 2006-09-26 | 196 | Safety Report 2006VX001335 Initial (Protocol 301) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 265 | 2006-10-04 | 197 | Safety Report 2006VX001413 Initial (Protocol 301) | Russell Katz, MD |
| 266 | 2006-10-10 | 198 | Safety Report 2006VX001564 Initial (Protocol 302) | Russell Katz, MD |
| 267 | 2006-10-12 | 199 | Safety Report 2006VX001413 FU1 (Protocol 301) | Russell Katz, MD |
| 268 | 2006-10-13 | 200 | Protocol Amendment: Change in Protocol -- Country Specific Addendums (Germany and Hungary) to the VRX-RET-E22-304 Protocol | Russell Katz, MD |
| 269 | 2006-10-17 | 201 | Protocol Amendment: New Investigator for 301 Protocol (Site Nos. 030, 033, 036, 041, 107, 202; revised site nos. 001, 004, 018, 025, 027; discontinue site nos. 006 and 023) | Russell Katz, MD |
| 270 | 2006-10-17 | 202 | Protocol Amendment: New Investigator for 303 Protocol (Site Nos. 001, 003, 004, 015, 041; revised site no. 025) | Russell Katz, MD |
| 271 | 2006-10-19 | 203 | Protocol Amendment: New Investigator for 302 Protocol (Site Nos. 252, 504, 804; revised site nos. 251, 401, 652, 851, 852, 853, 854; discontinue site no. 405) | Russell Katz, MD |
| 272 | 2006-10-27 | 204 | Safety Report 2006VX002111 Initial (Protocol 302) | Russell Katz, MD |
| 273 | 2006-10-31 | 205 | Protocol Amendment: New Investigator for 304 Protocol (Site No. 255) | Russell Katz, MD |
| 274 | 2006-10-31 | 206 | Protocol Amendment: Change in Protocol 302 (site specific addendums for site nos. 604 and 304) | Russell Katz, MD |
| 275 | 2006-11-06 | 207 | Safety Report 2006VX002111 FU1 (Protocol 302) | Russell Katz, MD |
| 276 | 2006-11-09 | 208 | Safety Report 2006VX002203 Initial (Protocol 302) | Russell Katz, MD |
| 277 | 2006-11-13 | 209 | Information Amendment: Clinical -- SAP for VRX-RET-E22-301 | Russell Katz, MD |
| 278 | 2006-11-13 | 210 | Information Amendment: Clinical -- SAP for VRX-RET-E22-302 | Russell Katz, MD |
| 279 | 2006-11-14 | 211 | Protocol Amendment: Change in Protocol VRX-RET-E22-304 -- Country Specific Addendum (Germany) | Russell Katz, MD |
| 280 | 2006-11-22 | 212 | Protocol Amendment: New Investigator Protocol 301 (Site No. 031; discontinue site no. 026) | Russell Katz, MD |
| 281 | 2006-11-22 | 213 | Protocol Amendment: New Investigator Protocol 302 (Site No. 801; discontinue site nos. 402 and 403) | Russell Katz, MD |

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|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 282 | 2006-11-22 | 214 | Protocol Amendment: New Investigator for Protocol 303 (Site Nos. 012, 014, 018, 021, 031, 036, 053) | Russell Katz, MD |
| 283 | 2006-11-30 | 215 | IND Safety Report 2006VX002307 Initial; Protocol VRX-RET-E22-301 | Russell Katz, MD |
| 284 | 2006-12-14 | 216 | Safety Report 2006VX002396 Initial (Protocol 304) | Russell Katz, MD |
| 285 | 2007-01-04 | 217 | Safety Report 2006VX002612 Initial (Protocol 302) | Russell Katz, MD |
| 286 | 2007-01-15 | 218 | Info Amendment Pharmacology Toxicology 13-Week Dog Study | Russell Katz, MD |
| 287 | 2007-01-16 | 219 | Safety Report 2006VX002396 FU 1 (Protocol 304) | Russell Katz, MD |
| 288 | 2007-01-17 | 220 | Safety Report 2006VX001263 FU 1 (Protocol 301) | Russell Katz, MD |
| 289 | 2007-01-18 | 221 | Safety Report 2006VX002307 FU 1 (Protocol 304) | Russell Katz, MD |
| 290 | 2007-01-19 | 222 | Fax: Safety Report 2007VX000145 Initial (Protocol 301) - 7-day | Russell Katz, MD |
| 291 | 2007-01-22 | 223 | Safety Report 2007VX000141 Initial (Protocol 301) | Russell Katz, MD |
| 292 | 2007-01-26 | 224 | Safety Report 2007VX000145 FU1 (Protocol 301) | Russell Katz, MD |
| 293 | 2007-02-01 | 225 | Safety Report 2006VX001335 FU1 (Protocol 301) | Russell Katz, MD |
| 294 | 2007-02-19 | 226 | Protocol Amendment: New Investigator for Protocol 301 (sites 53, 39,42, 20) | Russell Katz, MD |
| 295 | 2007-02-19 | 227 | Protocol Amendment: New Investigator for Protocol 302 (256, 507, 409, and 855) | Russell Katz, MD |
| 296 | 2007-02-20 | 228 | Protocol Amendment: New Investigator for Protocol 303 | Russell Katz, MD |
| 297 | 2007-02-23 | 229 | Fax: Safety Report 2007VX000145 FU2 (Protocol 301) | Russell Katz, MD |
| 298 | 2007-02-23 | 230 | Saftey Report 2007VX000509 Initial (Protocol 301) | Russell Katz, MD |
| 299 | 2007-02-28 | 231 | Safety Report 2007VX000141 FU1 (Protocol 301) | Russell Katz, MD |
| 300 | 2007-03-09 | 232 | General Correspondence: QTc Protocol - Request for Comments (Protocol 103) | Russell Katz, MD |
| 301 | 2007-03-13 | 233 | Safety Report 2007VX000669 Initial (Protocol 302) | Russell Katz, MD |
| 302 | 2007-03-14 | 281-T/C | T-Con to FDA regarding SN 218, 13 Wk dog study Protocol. Also low white blood cell counts and AE 2006VX00275. | Norm Hershkowitz, MD, from Art Rosenthal |
| 303 | 2007-03-15 | 234 | Fax: Safety Report 2007VX000145 FU3 (Protocol 301) | Russell Katz, MD |
| 304 | 2007-03-16 | 235 | Safety Report 2006VX001564 FU1 (Protocol 302) | Russell Katz, MD |

# Retigabine FDA Submission Log for Epilepsy
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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 305 | 2007-03-16 | 236 | Information Amendment: CMC update on API and Finished Product. | Russell Katz, MD |
| 306 | 2007-03-20 | 239-FDA | FDA e-mail Request for Completed ClinPharm Table (Protocol VRX-RET-E22-103) | Courtney Calder to A. Fernandez and A. Rosenthal |
| 307 | 2007-03-23 | 237 | Safety Report 2007VX000844 Initial (Protocol 303) | Russell Katz, MD |
| 308 | 2007-03-26 | 238 | Safety Report 2007VX000856 Initial (Protocol 301) | Russell Katz, MD |
| 309 | 2007-04-04 | 239 | Respond to Agency's fax request for information on Clinical Pharmacology on QTC | Russell Katz, MD |
| 310 | 2007-04-06 | 240 | Respond to Agency's fax request for information on Clinical Pharmacology/Tox on Dog Study (see S/N 218) | Russell Katz, MD |
| 311 | 2007-04-13 | 241 | Fax: Safety Report 2007VX001120 Initial (Protocol 304) | Russell Katz, MD |
| 312 | 2007-04-13 | 242 | Protocol Amendment: New Investigator for Protocol 303 (Site 039 and 012) | Russell Katz, MD |
| 313 | 2007-04-13 | 243 | Protocol Amendment: Update Investigator Information for Protocol 303 (Sites 002, 032, 004, 039, 017, 012 and 009) | Russell Katz, MD |
| 314 | 2007-04-13 | 244 | Protocol Amendment: Update Investigator Information for Protocol 301 (Sites 002, 032, 004, 039, 017, 012 and 009) | Russell Katz, MD |
| 315 | 2007-04-20 | 245 | Fax: Safety Report 2007VX000145 FU4 (Protocol 301) | Russell Katz, MD |
| 316 | 2007-04-26 | 246 | Safety Report 2007VX001142 Initial (Protocol 301) | Russell Katz, MD |
| 317 | 2007-04-24 | 247 | Safety Report 2007VX000856 FU1 (Protocol 301) | Russell Katz, MD |
| 318 | 2007-04-27 | 248 | Annual Report Oct 1 2005 - Sept 30 2006 | Russell Katz, MD |
| 319 | 2007-04-30 | 249 | IND Amendment: Pharmacology/Toxicology: Neonatal Mouse Study (preliminary results of PR2005-041) | Russell Katz, MD |
| 320 | 2007-05-01 | 250 | Gen.Corresp. Info Amendment Clinical Updates | Russell Katz, MD |
| 321 | 2007-05-01 | Tcon-FDA | 20070501- FDA Tcon - Request Info re AEs 2007VX0000145 + 2006VX002612 (Protocols 301 + 302) | Norm Hershkowitz, FDA and Art Rosenthal, VPNA |
| 322 | 2007-05-01 | 251 | Safety Report 2006VX002612 FU1 (Protocol 302) | Russell Katz, MD |
| 323 | 2007-05-01 | 252 | Safety Report 2006VX002612 FU2 (Protocol 302) | Russell Katz, MD |
| 324 | 2007-05-01 | 253 | Safety Report 2006VX002612 FU3 (Protocol 302) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 325 | 2007-05-01 | 254 | Safety Report 2007VX001120 FU1 (Protocol 304) | Russell Katz, MD |
| 326 | 2007-05-01 | 255-T/C | T-Con Request from FDA requesting information on 13-Wk study of N-acetyl metabolite of retigabine in dogs; as well as information on safety reports 2007VX00145 and 2006VX002612. | Norm Hershkowitz, MD, to Art Rosenthal |
| 327 | 2007-05-03 | 255 | Response to T-Con Request from FDA of 5/1/07 with regard 13-Wk study of N-acetyl metabolite of retigabine in dogs and to 2007VX000145 and 2006VX002612 (Protocols 301 and 302) | Russell Katz, MD |
| 328 | 2007-05-03 | 218-FDA | FDA letter dated 5/3/07, comments regarding SN 218 | Russell Katz, MD |
| 329 | 2007-05-03 | 256 | Safety Report 2006VX002396 FU 2 Hyponatraeami, Drug toxicity (Protocol 304) | Russell Katz, MD |
| 330 | 2007-05-04 | 257 | Safety Report 2006VX002396 FU 3 Hyponatraeami, Drug toxicity (Protocol 304) | Russell Katz, MD |
| 331 | 2007-05-04 | 258 | Safety Report 2007VX000632 Initial (Protocol 302) | Russell Katz, MD |
| 332 | 2007-05-04 | 259 | Safety Report 2007VX000638 Initial (Protocol 302) | Russell Katz, MD |
| 333 | 2007-05-04 | 260 | Safety Report 2007VX000927 Initial (Protocol 302) | Russell Katz, MD |
| 334 | 2007-05-09 | 261 | Protocol Amendment: Update Investigator Information for Protocol 303 (sites 001, 014, 025, 020) | Russell Katz, MD |
| 335 | 2007-05-09 | 262 | Protocol Amendment: Update Investigator Information - Protocol Number for 301 | Russell Katz, MD |
| 336 | 2007-05-10 | 263 | Safety Report 2007VX001305 Initial (Protocol 304) | Russell Katz, MD |
| 337 | 2007-05-14 | 264 | Safety Report 2006VX001102 FU1 (Protocol 301) | Russell Katz, MD |
| 338 | 2007-05-04 | 265 | Safety Report 2007VX000632 FU1 (Protocol 302) | Russell Katz, MD |
| 339 | 2007-05-16 | 232-FDA | FDA email regarding responses from QT team of March 9, 2007 submission - Request for comment (SN 232) Protocol 103 | Melina Griffis to A Rosenthal |
| 340 | 2007-05-16 | Tcon-FDA | FDA Telecon Minutes re: FDA request for follow-up info on 5 SAE cases | Russell Katz, MD |
| 341 | 2007-05-22 | 266 | Safety Report 2007VX001375 Initial (Protocol 302) | Russell Katz, MD |
| 342 | 2007-05-25 | 267 | Info Amendment: Response to the Agency's request for further information w/regard to SN 255 (Protocols 301 & 302) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 343 | 2007-05-25 | 268 | Safety Report 2007VX001429 Initial (Protocol 301) | Russell Katz, MD |
| 344 | 2007-05-25 | 269 | Safety Report 2007VX000638 FU1 (Protocol 302) | Russell Katz, MD |
| 345 | 2007-05-25 | 270 | Safety Report 2007VX000632 FU2 (Protocol 302) | Russell Katz, MD |
| 346 | 2007-05-25 | 271 | Safety Report 2007VX001428 Initial (Protocol 301) | Russell Katz, MD |
| 347 | 2007-05-29 | 267-FDA | Amendment to IND 53,950 for Tetigabine Tablets - Epilepsy (message) | Dr. Hershkowitz, FDA<br>Dwain Allen, VPNA |
| 348 | 2007-06-01 | 272 | Protocol Amendment: Update Investigator Information for Protocol 301 | Russell Katz, MD |
| 349 | 2007-06-01 | 273 | Protocol Amendment: Update Investigator Information for Protocol 303 | Russell Katz, MD |
| 350 | 2007-06-01 | 274 | Protocol Amendment: Update Investigator Information for Protocol 302 - sites 251 and 351 | Melina Griffis, R.Ph. |
| 351 | 2007-06-07 | 275 | Safety Report 2006VX001102 FU2 (Protocol 301) | Russell Katz, MD |
| 352 | 2007-06-12 | 276 | Safety Report 2007VX001429 FU1 (Protocol 301) | Russell Katz, MD |
| 353 | 2007-06-08 | 277 | Protocol Amendment: QTC Amendment - (Response to FDA email of May 16, 2007) Protocol 103 | Russell Katz, MD |
| 354 | 2007-06-08 | 278 | Safety Report 2007VX001428 FU1 (Protocol 301) | Russell Katz, MD |
| 355 | 2007-06-08 | 279 | Safety Report 2007VX000669 FU1 (Protocol 302) | Russell Katz, MD |
| 356 | 2007-06-08 | 280 | Safety Report 2007VX001513 Initial (Protocol 301) | Russell Katz, MD |
| 357 | 2007-06-13 | 281 | Safety Report 2007VX001527 Initial (Protocol 304) | Russell Katz, MD |
| 358 | 2007-06-18 | 282 | Safety Report 2007VX001597 Initial (Protocol 302) | Russell Katz, MD |
| 359 | 2007-06-20 | 283 | Safety Report 2007VX000844 FU1 (Protocol 303) | Russell Katz, MD |
| 360 | 2007-06-20 | 284 | Safety Report 2007VX001429 FU2 (Protocol 301) | Russell Katz, MD |
| 361 | 2007-06-20 | 285 | Safety Report 2007VX001598 Initial (Protocol 301) | Russell Katz, MD |
| 362 | 2007-06-20 | 286 | Fax: Safety Report 2007VX001646 Initial (Protocol 301) | Russell Katz, MD |
| 363 | 2007-06-21 | Email-FDA | FDA Emails- SAP Acceptability for Protocols 301 and 302 | Melina Griffis, FDA<br>A.Rosenthal, VPNA |
| 364 | 2007-06-22 | 287 | Protocol Amendment: Country Specific Addendum 1 for Germany (302) | Russell Katz, MD |
| 365 | 2007-06-26 | 288 | Safety Report 2006VX001102 FU3 (Protocol 301) | Russell Katz, MD |
| 366 | 2007-06-26 | 289 | Safety Report 2007VX001597 FU1 (Protocol 302) | Russell Katz, MD |
| 367 | 2007-06-29 | 290 | Safety Report 2007VX001659 Initial (Protocol 302) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 368 | 2007-06-29 | 291 | Protocol Amendment: New Investigator Information for VRX-RET-E22-103 (QTc) Study (Site 001) | Russell Katz, MD |
| 369 | 2007-07-03 | 292 | Safety Report 2007VX001748 Initial (Protocol 303) | Russell Katz, MD |
| 370 | 2007-07-06 | 293 | Protocol Amendment: New Investigator for Protocol 304 sites 409 and 507 | Russell Katz, MD |
| 371 | 2007-07-06 | 294 | Protocol Amendment: Updated Investigator Information for 301 site 051 | Russell Katz, MD |
| 372 | 2007-07-06 | 295 | Protocol Amendment: New Investigator/Investigator Updates for Protocol 303 (sites 051, and 039) updates to 051. | Russell Katz, MD |
| 373 | 2007-07-06 | 296 | Protocol Amendment: New Investigator and Investigator Updates Protocol 302 (sites 706) updates (852, 855, 256) | Russell Katz, MD |
| 374 | 2007-07-06 | 297 | Protocol Amendment: Change in Protocol (VRX-RET-E22-302) Addendum 4 | Russell Katz, MD |
| 375 | 2007-07-06 | 298 | Protocol Amendment: General Correspondence and Change in Protocols VRX-RET-E22-303 and 304. (responding to FDA letter dated 5/3/07 regarding SN 218 (SN 240 and 255). | Russell Katz, MD |
| 376 | 2007-07-06 | 299 | Safety Report 2007VX001597 FU2 (Protocol 302) | Russell Katz, MD |
| 377 | 2007-07-06 | 300 | Safety Report 2007VX001749 Initial (Protocol 301) | Russell Katz, MD |
| 378 | 2007-07-11 | 301 | Safety Report 2007VX000638 FU2 (Protocol 302) | Russell Katz, MD |
| 379 | 2007-07-12 | 302 | Safety Report 2007VX000509 FU1 (Protocol 301) | Russell Katz, MD |
| 380 | 2007-07-12 | 303 | Safety Report 2007VX000856 FU2 (Protocol 301) | Russell Katz, MD |
| 381 | 2007-07-17 | 304 | Safety Report 2007VX001748 FU1 (Protocol 303) | Russell Katz, MD |
| 382 | 2007-07-18 | 305 | Protocol Amendment: New Investigator (site 411), Protocol 302 | Russell Katz, MD |
| 383 | 2007-07-18 | 306 | Protocol Amendment: New Investigator, Investigator Update (Protocol 304) site 301 | Russell Katz, MD |
| 384 | 2007-07-20 | 307 | General Correspondence - Pre-NDA Mtg (Type B) July 20, 2007 | Russell Katz, MD |
| 385 | 2007-07-20 | 308 | Safety Report 2007VX000018 Initial (Protocol 301) | Russell Katz, MD |
| 386 | 2007-07-20 | 309 | Safety Report 2007VX001749 FU1 (Protocol 301) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 387 | 2005-07-21 | Tcon-FDA | T-Con Meeting Minutes re: letters of May 13, 2005 and June 29, 2005 | C. Calder, FDA |
| 388 | 2007-07-24 | 310 | Safety Report 2007VX001853 Initial (Protocol 301) | Russell Katz, MD |
| 389 | 2007-07-25 | 311 | Safety Report 2007VX001898 Initial (Protocol 303) | Russell Katz, MD |
| 390 | 2007-07-27 | 312 | Protocol Amendment: Investigator Updates - Protocol 301 (sites 003, 018, 025, and 030) | Russell Katz, MD |
| 391 | 2007-07-31 | 313 | Protocol Amendment: New Investigator - and Investigator Updates for Protocol VRX-RET-E22-303 (new site 030) (updates sites 003, 018, 025 and 027) | Russell Katz, MD |
| 392 | 2007-07-31 | 314 | Safety Report 2007VX001901 Initial (Protocol 304) | Russell Katz, MD |
| 393 | 2007-07-31 | 315 | Safety Report 2006VX002111 FU2 (Protocol 302) | Russell Katz, MD |
| 394 | 2007-07-31 | 316 | Protocol Amendment: New Investigator - Protocol 301and 303 (site 053) Dr William Murphy replacing Dr. Samuel Wiebe | Russell Katz, MD |
| 395 | 2007-07-31 | 317 | Protocol Amendment: New Investigator - Protocol 303 (Site 013) | Russell Katz, MD |
| 396 | 2007-07-31 | 318 | Protocol Amendment: New Investigator - Protocol 302 (site 408) | Russell Katz, MD |
| 397 | 2007-08-02 | 319 | Safety Report 2007VX001527 FU1 (Protocol 304) | Russell Katz, MD |
| 398 | 2007-08-03 | Email-FDA | FDA Email re Pre-NDA Meeting Confirmation | Melina Griffis, FDA<br>A.Rosenthal, VPNA |
| 399 | 2007-08-03 | 320 | Safety Report 2007VX000632 FU3 (Protocol 302) | Russell Katz, MD |
| 400 | 2007-08-08 | 321 | Safety Report 2007VX000638 FU 3 (Protocol 302) | Russell Katz, MD |
| 401 | 2007-08-08 | 322 | Safety Report 2007VX001305 FU 1 (Protocol 304) | Russell Katz, MD |
| 402 | 2007-08-08 | 323 | Safety Report 2007VX001971 Initial (Protocol 303) | Russell Katz, MD |
| 403 | 2007-08-10 | 324 | Safety Report 2007VX001749 FU2 (Protocol 301) | Russell Katz, MD |
| 404 | 2007-08-10 | 325 | Safety Report 2007VX002010 Initial (Protocol 303) | Russell Katz, MD |
| 405 | 2007-08-10 | 326 | Safety Report 2007VX000018 FU1 (Protocol 301) | Russell Katz, MD |
| 406 | 2007-08-13 | 327 | Safety Report 2007VX001597 FU3 (Protocol 302) | Russell Katz, MD |
| 407 | 2007-08-14 | 328 | Safety Report 2007VX001659 FU1 (Protocol 302) | Russell Katz, MD |
| 408 | 2007-08-15 | 329 | Safety Report 2007VX001513 FU1 (Protocol 301) | Russell Katz, MD |
| 409 | 2007-08-17 | 330 | Protocol Amendment: New Investigator for (Portocol 302) sites 952 and 953 | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 410 | 2007-08-17 | 331 | Protocol Amendment: New Investigator/Investigator Updates for (Protocol 301 and 303 site 027) and (update Protocol 301 site 027). | Russell Katz, MD |
| 411 | 2007-08-17 | 332 | Safety Report 2007VX000856 FU3 (Protocol 301) | Russell Katz, MD |
| 412 | 2007-08-21 | 333 | Safety Report 2007VX002097 Initial (Protocol 303) | Russell Katz, MD |
| 413 | 2007-08-23 | 334 | Safety Report 2007VX000018 FU2 (Protocol 301) | Russell Katz, MD |
| 414 | 2007-08-23 | 335 | Safety Report 2007VX001749 FU3 (Protocol 301) | Russell Katz, MD |
| 415 | 2007-08-23 | 336 | Protocol Amendment: Site Specific Addendum for Protocol VRX-RET-E22-303 (Sites 1,2,9,14, and 25) | Russell Katz, MD |
| 416 | 2007-08-28 | 337 | Safety Report 2007VX001853 FU1 (Protocol 301) | Russell Katz, MD |
| 417 | 2007-08-30 | 338 | Protocol Amendment: New Protocol - VRX-RET-E22-102 - August 21 2007 (Liver) | Russell Katz, MD |
| 418 | 2007-08-31 | 339 | Protocol Amendment VRX-RET-E22-101 | Russell Katz, MD |
| 419 | 2007-08-31 | 340 | Safety Report 2007VX002169 Initial (Protocol 304) | Russell Katz, MD |
| 420 | 2007-08-31 | 341 | Safety Report 2007VX002193 Initial (Protocol 302) | Russell Katz, MD |
| 421 | 2007-08-31 | 342 | Safety Report 2007VX001725 Initial (Protocol 301) | Russell Katz, MD |
| 422 | 2007-09-06 | 343 | Safety Report 2007VX002209 Initial (Protocol 301) | Russell Katz, MD |
| 423 | 2007-09-10 | 344 | Pre-NDA Meeting - Briefing Package | Russell Katz, MD |
| 424 | 2007-09-10 | 345 | Safety Report 2006VX002203 FU1 (Protocol 302) | Russell Katz, MD |
| 425 | 2007-09-12 | Email-FDA | FDA email request for elec-copy of Pre-NDA Package | Melina Griffis, FDA<br>A.Rosenthal, VPNA |
| 426 | 2007-09-14 | 346 | Additional Information - Response to FDA's request on the Urinary Retention pts. (duplicate copies on file) | Russell Katz, MD |
| 427 | 2007-09-14 | 347 | Safety Report 2007VX001527 FU2 (Protocol 304) | Russell Katz, MD |
| 428 | 2007-09-17 | 348 | Safety Report 2007VX002279 Initial (Protocol 304) | Russell Katz, MD |
| 429 | 2007-09-18 | 349 | Information Amendment - Investigator's Brochure update Sept 13, 2007 (GKE 841) | Russell Katz, MD |
| 430 | 2007-09-18 | 350 | Safety Report 2007VX001375 FU1 (Protocol 302) | Russell Katz, MD |
| 431 | 2007-09-18 | 351 | Safety Report 2006VX000342 Initial (Protocol 301) | Russell Katz, MD |
| 432 | 2007-09-18 | 352 | General: Cross-Reference Authorization for Dr. Ronald Aung-Din - Compassionate Use (Protocols 301 & 303) | Russell Katz, MD |
| 433 | 2007-09-21 | 353 | Safety Report 2007VX002193 FU1 (Protocol 302) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 434 | 2007-09-25 | 277-FDA | FDA Email - QTc Comments/Response from FDA (Protocols 301 and 302) | Melina Griffis, FDA<br>A.Rosenthal, VPNA |
| 435 | 2007-09-28 | 354 | Protocol Amendment: New Investigators for Protocol 303 (Sites 0389 and 042) | Russell Katz, MD |
| 436 | 2007-09-28 | 355 | Safety Report 2007VX001598 FU1 (Protocol 301) | Russell Katz, MD |
| 437 | 2007-09-28 | 356 | Safety Report 2007VX002346 Initial (Protocol 302) | Russell Katz, MD |
| 438 | 2007-09-28 | 357 | Safety Report 2007VX002354 Initial (Protocol 301) | Russell Katz, MD |
| 439 | 2007-09-28 | 358 | Safety Report 2007VX001120 FU2 (Protocol 304) | Russell Katz, MD |
| 440 | 2007-10-02 | 359 | Protocol Amendment: New Investigator and Investigator Update for Protocol 302 (Site 553, 554, 555, 556, and 558) | Russell Katz, MD |
| 441 | 2007-10-02 | 360 | Safety Report 2007VX001901 FU1 (Protocol 304) | Russell Katz, MD |
| 442 | 2007-10-02 | 361 | Safety Report 2007VX000018 FU3 (Protocol 301) | Russell Katz, MD |
| 443 | 2007-10-02 | 362 | Safety Report 2007VX001749 FU4 (Protocol 301) | Russell Katz, MD |
| 444 | 2007-10-02 | 363 | Safety Report 2007VX000844 FU2 (Protocol 303) - 7-Day | Russell Katz, MD |
| 445 | 2007-10-03 | 364 | Safety Report 2007VX001898 FU1 (Protocol 303) | Russell Katz, MD |
| 446 | 2007-10-03 | 365 | Safety Report 2007VX000509 FU2 (Protocol 301) | Russell Katz, MD |
| 447 | 2007-10-03 | 366 | Safety Report 2007VX001375 FU2 (Protocol 302) | Russell Katz, MD |
| 448 | 2007-10-07 | Email-FDA | FDA Email - Response to Pre-NDA Questions | Melina Griffis, FDA<br>A.Rosenthal, VPNA |
| 449 | 2007-10-05 | 367 | Safety Report 2007VX002097 FU1 (Protocol 303) | Russell Katz, MD |
| 450 | 2007-10-05 | 368 | Safety Report 2007VX002461 Initial (Protocol 303) - 7-Day | Russell Katz, MD |
| 451 | 2007-10-05 | 369 | Safety Report 2007VX002209 FU1 (Protocol 301) | Russell Katz, MD |
| 452 | 2007-10-05 | 370 | Safety Report 2007VX001659 FU2 (Protocol 302) | Russell Katz, MD |
| 453 | 2007-10-08 | 371 | Safety Report 2007VX002354 FU1 (Protocol 301) | Russell Katz, MD |
| 454 | 2007-10-11 | 372 | Protocol Amendment: VRX-RET-E22-101, Amendment 3 | Russell Katz, MD |
| 455 | 2007-10-11 | 373 | Protocol Amendment: VRX-RET-E22-102, Amendment 1 | Russell Katz, MD |
| 456 | 2007-10-11 | 374 | Safety Report 2007VX001978 Initial (Protocol 302) | Russell Katz, MD |
| 457 | 2007-10-11 | 375 | Safety Report 2006VX001102 FU4 (Protocol 301) | Russell Katz, MD |
| 458 | 2007-10-12 | 376 | Safety Report 2007VX002279 FU1 (Protocol 304) | Russell Katz, MD |
| 459 | 2007-10-15 | 377 | Safety Report 2007VX000509 FU3 (Protocol 301) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 460 | 2007-10-16 | 378 | Safety Report 2006VX001263 FU2 (Protocol 301) | Russell Katz, MD |
| 461 | 2007-10-17 | 379 | Protocol Amendment - Amendment 3 for 302 | Russell Katz, MD |
| 462 | 2007-10-17 | 380 | Information Amendment: CMC update on Manufacturer of Finished Product. | Russell Katz, MD |
| 463 | 2007-10-18 | 381 | Safety Report 2007VX001527 FU3 (Protocol 304) | Russell Katz, MD |
| 464 | 2007-10-22 | 382 | Safety Report 2007VX001597 FU4 (Protocol 302) | Russell Katz, MD |
| 465 | 2007-10-24 | 383 | Safety Report 2007VX000018 FU4 (Protocol 301) | Russell Katz, MD |
| 466 | 2007-10-24 | 384 | Safety Report 2007VX000509 FU4 (Protocol 301) | Russell Katz, MD |
| 467 | 2007-10-24 | 385 | Safety Report 2007VX001749 FU5 (Protocol 301) | Russell Katz, MD |
| 468 | 2007-10-25 | 386 | Safety Report 2006VX000894 Initial (Protocol 301) | Russell Katz, MD |
| 469 | 2007-10-29 | 387 | Safety Report 2006VX001335 FU2 (Protocol 301) | Russell Katz, MD |
| 470 | 2007-10-29 | 388 | Safety Report 2007VX002346 FU1 (Protocol 302) | Russell Katz, MD |
| 471 | 2007-10-30 | 389 | Safety Report 2007VX002597 Initial (Protocol 301) | Russell Katz, MD |
| 472 | 2007-11-02 | 390 | Safety Report 2007VX002279 FU2 (Protocol 304) | Russell Katz, MD |
| 473 | 2007-11-02 | 391 | Safety Report 2007VX001898 FU2 (Protocol 303) | Russell Katz, MD |
| 474 | 2007-11-02 | 392 | Safety Report 2007VX000844 FU3 (Protocol 303) | Russell Katz, MD |
| 475 | 2007-11-05 | 393 | Safety Report 2007VX000669 FU2 (Protocol 302) | Russell Katz, MD |
| 476 | 2007-11-06 | 394 | Safety Report 2007VX002663 Initial (Protocol 303) | Russell Katz, MD |
| 477 | 2007-11-09 | 395 | Safety Report 2007VX002658 Initial (Protocol 304) | Russell Katz, MD |
| 478 | 2007-11-09 | 396 | Safety Report 2007VX002279 FU3 (Protocol 304) | Russell Katz, MD |
| 479 | 2007-11-09 | 397 | Safety Report 2007VX002097 FU2 (Protocol 303) | Russell Katz, MD |
| 480 | 2007-11-15 | 398 | Safety Report 2007VX002461 FU1 to 7-day (Protocol 303) | Russell Katz, MD |
| 481 | 2007-11-19 | 399 | Safety Report 2007VX000844 FU4 (Protocol 303) | Russell Katz, MD |
| 482 | 2007-11-19 | 400 | Safety Report 2007VX002658 FU1 (Protocol 304) | Russell Katz, MD |
| 483 | 2007-11-20 | 401 | Protocol Amendment - New Investigator for 303 (site 033) | Russell Katz, MD |
| 484 | 2007-11-20 | 402 | Safety Report 2007VX002597FU1 (Protocol 301) | Russell Katz, MD |
| 485 | 2007-11-20 | 403 | Safety Report 2007VX002010 FU1 (Protocol 303) | Russell Katz, MD |
| 486 | 2007-11-20 | 404 | Safety Report 2007VX002169 FU1 (Protocol 302) | Russell Katz, MD |
| 487 | 2007-11-21 | 405 | Safety Report 2007VX001749 FU6 (Protocol 301) | Russell Katz, MD |
| 488 | 2007-11-30 | 406 | Annual Report 2007 | Russell Katz, MD |
| 489 | 2007-11-30 | 407 | Safety Report 2007VX001659 FU3 (Protocol 302) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 490 | 2007-12-03 | 408 | Protocol Amendment - New Protocol for 108 | Russell Katz, MD |
| 491 | 2007-12-03 | 409 | Safety Report 2007VX002794 Initial (Protocol 302) | Russell Katz, MD |
| 492 | 2007-12-03 | 410 | Safety Report 2007VX002825 Initial (Protocol 302) | Russell Katz, MD |
| 493 | 2007-12-05 | Tcon-FDA | T-Con re: Request to FDA for Information on Aes | N. Hershkowitz, FDA |
| 494 | 2007-12-06 | 411 | Protocol Amendment - New Protocol for 104 | Russell Katz, MD |
| 495 | 2007-12-06 | 412 | Protocol Amendment - New Protocol for 105 | Russell Katz, MD |
| 496 | 2007-12-06 | 413 | Protocol Amendment - New Protocol for 106 | Russell Katz, MD |
| 497 | 2007-12-06 | 414 | Protocol Amendment - New Protocol for 107 | Russell Katz, MD |
| 498 | 2007-12-07 | 415 | Response to FDA Request for Further Information (Protocol 103) | Russell Katz, MD |
| 499 | 2007-12-11 | 416 | Safety Report 2007VX002279 FU4 (Protocol 304) | Russell Katz, MD |
| 500 | 2007-12-12 | 417 | Safety Report 2007VX002658 FU2 (Protocol 304) | Russell Katz, MD |
| 501 | 2007-12-12 | 418 | Information Amendment: FDA Request for Further Inf. (2007VX002658) | Russell Katz, MD |
| 502 | 2007-12-13 | 419 | Safety Report 2007VX002893 Initial (Protocol 303) | Russell Katz, MD |
| 503 | 2007-12-13 | 420 | Safety Report 2007VX002794 FU1 (Protocol 302) | Russell Katz, MD |
| 504 | 2007-12-13 | 421 | Safety Report 2007VX002919 Initial (Protocol 302) | Russell Katz, MD |
| 505 | 2007-12-13 | 422 | Safety Report 2007VX001120 FU3 (Protocol 304) | Russell Katz, MD |
| 506 | 2007-12-13 | 423 | Safety Report 2007VX001978 FU1 (Protocol 302) | Russell Katz, MD |
| 507 | 2007-12-17 | 424 | Safety Report 2007VX001659 FU4 (Protocol 302) | Russell Katz, MD |
| 508 | 2007-12-20 | 425 | Safety Report 2007VX000632 FU4 (Protocol 302) | Russell Katz, MD |
| 509 | 2007-12-20 | 426 | Safety Report 2007VX001375 FU3 (Protocol 302) | Russell Katz, MD |
| 510 | 2007-12-20 | 427 | Safety Report 2007VX002955 Initial (Protocol 303) | Russell Katz, MD |
| 511 | 2007-12-20 | 428 | Safety Report 2007VX001597 FU5 (Protocol 302) | Russell Katz, MD |
| 512 | 2007-12-21 | 429 | Safety Report 2007VX002825 FU1 (Protocol 302) | Russell Katz, MD |
| 513 | 2007-12-21 | 430 | Safety Report 2007VX003015 Initial (Protocol 302) | Russell Katz, MD |
| 514 | 2007-12-21 | 431 | Safety Report 2007VX002794 FU2 (Protocol 302) | Russell Katz, MD |
| 515 | 2007-12-21 | 432 | Safety Report 2007VX002841 Initial (Protocol 302) | Russell Katz, MD |
| 516 | 2007-12-21 | 433 | Safety Report 2007VX003020 Initial (Protocol 303) | Russell Katz, MD |
| 517 | 2007-12-21 | 434 | Safety Report 2006VX002203 FU2 (Protocol 302) | Russell Katz, MD |
| 518 | 2007-12-21 | 435 | Safety Report 2007VX002919 FU1 (Protocol 302) | Russell Katz, MD |
| 519 | 2007-12-21 | 436 | Safety Report 2007VX002985 Initial (Protocol 304) | Russell Katz, MD |
| 520 | 2007-12-21 | 437 | Safety Report 2007VX003007 Initial (Protocol 303) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 521 | 2007-12-27 | 438 | Safety Report 2007VX002169 FU2 (Protocol 302) | Russell Katz, MD |
| 522 | 2008-01-02 | 439 | Safety Report 2007VX001513 FU2 (Protocol 301) | Russell Katz, MD |
| 523 | 2008-01-03 | 440 | Safety Report 2007VX001901 FU2 (Protocol 304) | Russell Katz, MD |
| 524 | 2008-01-04 | 441 | Safety Report 2007VX002346 FU2 (Protocol 302) - Infection | Russell Katz, MD |
| 525 | 2008-01-04 | 442 | Statistical Analysis Plan for Protocol VRX-RET-E22-301 - Amendment 1 | Russell Katz, MD |
| 526 | 2008-01-04 | 443 | Safety Report 2007VX003035 Initial (Protocol 301) | Russell Katz, MD |
| 527 | 2008-01-08 | 444 | Safety Report 2007VX003007 FU1 (Protocol 303) | Russell Katz, MD |
| 528 | 2008-01-11 | 445 | Safety Report 2007VX000018 FU5 (Protocol 301) | Russell Katz, MD |
| 529 | 2008-01-11 | 446 | Safety Report 2007VX001749 FU7 (Protocol 301) | Russell Katz, MD |
| 530 | 2008-01-17 | 447 | Safety Report 2007VX002658 FU3 (Protocol 304) | Russell Katz, MD |
| 531 | 2008-01-17 | 448 | Safety Report 2007VX002841 FU1 (Protocol 302) | Russell Katz, MD |
| 532 | 2008-01-17 | 449 | Safety Report 2008VX000052 Initial (Protocol 301) | Russell Katz, MD |
| 533 | 2008-01-17 | 450 | Safety Report 2007VX002955 FU1 (Protocol 303) | Russell Katz, MD |
| 534 | 2008-01-17 | 451 | Safety Report 2007VX002995 Initial (Protocol 303) | Russell Katz, MD |
| 535 | 2008-01-17 | 452 | Safety Report 2008VX000087 Initial (Protocol 301) | Russell Katz, MD |
| 536 | 2008-01-17 | | General Correspondence-Proposed Manufacturing Process Validation Strategy (filed under Miscellaneous) | Kathleen D. Culver,RIC |
| 537 | 2008-01-18 | 453 | Safety Report 2008VX000069 Initial (Protocol 301) | Russell Katz, MD |
| 538 | 2008-01-21 | 454 | Safety Report 2007VX002354 FU2 (Protocol 301) | Russell Katz, MD |
| 539 | 2008-01-22 | 455 | Safety Report 2007VX002995 FU1 (Protocol 303) | Russell Katz, MD |
| 540 | 2008-01-22 | 456 | Safety Report 2008VX000108 Initial (Protocol 302) | Russell Katz, MD |
| 541 | 2008-01-23 | 457 | Safety Report 2007VX002841 FU2 (Protocol 302) | Russell Katz, MD |
| 542 | 2008-01-24 | 458 | Safety Report 2008VX000052 FU1 (Protocol 301) | Russell Katz, MD |
| 543 | 2008-01-24 | 459 | Safety Report 2008VX000087 FU1 (Protocol 301) | Russell Katz, MD |
| 544 | 2008-01-24 | 460 | Safety Report 2008VX000127 Initial (Protocol 301) | Russell Katz, MD |
| 545 | 2008-01-24 | 461 | Safety Report 2007VX003020 FU1 (Protocol 303) | Russell Katz, MD |
| 546 | 2008-01-28 | 462 | Statistical Analysis Plan for Protocol VRX-RET-E22-301 - Amendment 2 | Russell Katz, MD |
| 547 | 2008-01-29 | 463 | Safety Report 2008VX000088 Initial (Protocol 301) | Russell Katz, MD |
| 548 | 2008-01-29 | 464 | Safety Report 2007VX003035 FU1 (Protocol 301) | Russell Katz, MD |
| 549 | 2008-01-29 | 465 | Safety Report 2008VX000087 FU2 (Protocol 301) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 550 | 2008-01-29 | 466 | Safety Report 2007VX002658 FU4 (Protocol 304) | Russell Katz, MD |
| 551 | 2008-01-29 | 467 | Safety Report 2008VX000125 Initial (Protocol 303) | Russell Katz, MD |
| 552 | 2008-01-29 | 468 | Safety Report 2008VX000127 FU1 (Protocol 301) | Russell Katz, MD |
| 553 | 2008-01-29 | 469 | Safety Report 2007VX002995 FU2 (Protocol 303) | Russell Katz, MD |
| 554 | 2008-01-29 | 470 | Safety Report 2007VX003007 FU2 (Protocol 303) | Russell Katz, MD |
| 555 | 2008-01-30 | 471 | Safety Report 2007VX002794 FU3 (Protocol 302) | Russell Katz, MD |
| 556 | 2008-01-30 | 472 | Safety Report 2007VX002893 FU1 (Protocol 303) | Russell Katz, MD |
| 557 | 2008-01-30 | 473 | Safety Report 2008VX000173 Intial (Protocol 301) | Russell Katz, MD |
| 558 | 2008-01-30 | 474 | Safety Report 2008VX000174 Initial (Protocol 301) | Russell Katz, MD |
| 559 | 2008-01-30 | 475 | Safety Report 2008VX000052 FU2 (Protocol 301) | Russell Katz, MD |
| 560 | 2008-01-30 | 476 | Safety Report 2007VX002919 FU2 (Protocol 302) | Russell Katz, MD |
| 561 | 2008-01-31 | 477 | Safety Report 2007VX002841 FU3 (Protocol 302) | Russell Katz, MD |
| 562 | 2008-02-01 | 478 | Safety Report 2007VX002658 FU5 (Protocol 304) | Russell Katz, MD |
| 563 | 2008-02-01 | 479 | Protocol Amendment: New Investigator and Investigator Update (Protocol 301) sites 035, 011, 013 020, 036, 041, 052. | Russell Katz, MD |
| 564 | 2008-02-01 | 480 | Protocol Amendment: New Investigator and Investigator Update (Protocol 303) sites 035, 011, 013 020, 041. | Russell Katz, MD |
| 565 | 2008-02-06 | 481 | Safety Report 2007VX002841 FU4 (Protocol 302) | Russell Katz, MD |
| 566 | 2008-02-06 | 482 | Safety Report 2007VX002794 FU4 (Protocol 302) | Russell Katz, MD |
| 567 | 2008-02-06 | 483 | Safety Report 2008VX000127 FU2 (Protocol 301) | Russell Katz, MD |
| 568 | 2008-02-06 | 484 | Safety Report 2007VX002354 FU3 (Protocol 301) | Russell Katz, MD |
| 569 | 2008-02-08 | 485 | Safety Report 2008VX000231 Initial (Protocol 303) | Russell Katz, MD |
| 570 | 2008-02-08 | 486 | Safety Report 2007VX002985 FU1 (Protocol 304) | Russell Katz, MD |
| 571 | 2008-02-08 | 487 | Safety Report 2008VX000125 FU1 (Protocol 303) | Russell Katz, MD |
| 572 | 2008-02-11 | 488 | Safety Report 2008VX000108 FU1 (Protocol 302) | Russell Katz, MD |
| 573 | 2008-02-11 | 489 | Safety Report 2007VX002893 FU2 (Protocol 303) | Russell Katz, MD |
| 574 | 2008-02-19 | 490 | Safety Report 2007VX002995 FU3 (Protocol 303) | Russell Katz, MD |
| 575 | 2008-02-20 | 491 | Safety Report 2007VX003007 FU3 (Protocol 303) | Russell Katz, MD |
| 576 | 2008-02-22 | 492 | Safety Report 2007VX001978 FU2 (Protocol 302) | Russell Katz, MD |
| 577 | 2008-02-28 | 493 | Safety Report 2007VX002658 FU6 (Protocol 304) | Russell Katz, MD |
| 578 | 2008-02-28 | 494 | Safety Report 2007VX003015 FU1 (Protocol 302) | Russell Katz, MD |
| 579 | 2008-02-28 | 495 | Safety Report 2007VX003007 FU4 (Protocol 303) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 580 | 2008-03-03 | 496 | Safety Report 2008VX000406 Initial (Protocol 303) | Russell Katz, MD |
| 581 | 2008-03-04 | 497 | Safety Report 2007VX002841 FU5 (Protocol 302) | Russell Katz, MD |
| 582 | 2008-03-05 | 498 | Protocol Amendment (Amendment 1 - Addendum 2 for 303) - Country Specific - United States to study urinary crystals | Russell Katz, MD |
| 583 | 2008-03-07 | 499 | Protocol Amendment - Investigator Updates (Protocol 302- sites 301, 302, 303, 304, 451, 552, 557, 602, 701, 702, 703, 706, 853) | Russell Katz, MD |
| 584 | 2008-03-11 | 500 | Safety Report 2008VX000406 FU1 (Protocol 303) | Russell Katz, MD |
| 585 | 2008-03-11 | 501 | Safety Report 2007VX002995 FU4 (Protocol 303) | Russell Katz, MD |
| 586 | 2008-03-12 | 502 | Protocol Amendment - Investigator Updates (Protocol 304, sites 351, 451, 453, 705, 851 and 953) | Russell Katz, MD |
| 587 | 2008-03-14 | 503 | Safety Report 2007VX002825 FU2 (Protocol 302) | Russell Katz, MD |
| 588 | 2008-03-14 | 504 | Protocol Amendment: New Investigator (Protocol 105) | Russell Katz, MD |
| 589 | 2008-03-14 | 505 | Protocol Amendment: New Investigator (Protocol 106) | Russell Katz, MD |
| 590 | 2008-03-14 | 506 | Protocol Amendment: New Investigator (Protocol 108) | Russell Katz, MD |
| 591 | 2008-03-14 | 507 | Protocol Amendment: New Investigator (Protocol 102) | Russell Katz, MD |
| 592 | 2008-03-14 | 508 | Protocol Amendment: New Investigator (Protocol 104) | Russell Katz, MD |
| 593 | 2008-03-17 | 509 | Protocol Amendment: New Investigator (Protocol 107) | Russell Katz, MD |
| 594 | 2008-03-18 | 510 | Information Amendment: Clinical - Press Release | Russell Katz, MD |
| 595 | 2008-03-19 | 511 | Safety Report 2007VX003015 FU2 (Protocol 302) | Russell Katz, MD |
| 596 | 2008-03-20 | 512 | Safety Report 2008VX000727 Initial (Protocol 108) | Russell Katz, MD |
| 597 | 2008-03-24 | 513 | General Correspondence: Name Change to KOTIGA™ (retigabine) | Russell Katz, MD |
| 598 | 2008-03-25 | 514 | Safety Report 2008VX000718 Initial (Protocol 302) | Russell Katz, MD |
| 599 | 2008-03-25 | 515 | Protocol Amendment VRX-RET-E22-107, Amendment 2 | Russell Katz, MD |
| 600 | 2008-03-25 | 516 | Protocol Amendment VRX-RET-E22-108, Amendment 1 | Russell Katz, MD |
| 601 | 2008-03-31 | 517 | Safety Report 2007VX002995 FU5 (Protocol 303) | Russell Katz, MD |
| 602 | 2008-04-01 | 518 | Safety Report 2007VX002841 FU6 (Protocol 302) | Russell Katz, MD |
| 603 | 2008-04-01 | 519 | Safety Report 2008VX000750 Initial (Protocol 108) | Russell Katz, MD |
| 604 | 2008-04-04 | 520 | Safety Report 2008VX000727 FU1 (Protocol 108) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 605 | 2008-04-07 | 521 | Safety Report 2007VX003015 FU3 (Protocol 302) | Russell Katz, MD |
| 606 | 2008-04-08 | 522 | Safety Report 2008VX000406 FU2 (Protocol 303) | Russell Katz, MD |
| 607 | 2008-04-09 | Tcon-FDA | FDA T-Con re: AE Cardiac Safety Report for 2008VX000727, 2005VX000676, 2007VX001598 | Steven Dinsmore MD, FDA Art Rosenthal, VPNA |
| 608 | 2008-04-09 | 523 | Info Amendment: FDA Request for Further Information: Urinary Retention case update submitted to FDA (to SN 346) | Russell Katz, MD |
| 609 | 2008-04-09 | Email-523-Revisions | Email with Revisions to report sent earlier in the day - Valeant to FDA forward Urinary Retention case update (to SN346) | Steven Dinsmore MD, FDA Art Rosenthal, VPNA |
| 610 | 2008-04-09 | 524 | Safety Report 2006VX002612 FU4 (Protocol 302) | Russell Katz, MD |
| 611 | 2008-04-10 | 525 | Information Amendment: CMC (batch scale up-commecial image) | Russell Katz, MD |
| 612 | 2008-04-10 | 526 | Statistical Analysis Plan for Protocol VRX-RET-E22-302, Amendment 1 (update to SN 210) | Russell Katz, MD |
| 613 | 2008-06-21 | 526-FDA | FDA email re SAP for Protocol 302 | Melina Griffis, FDA |
| 614 | 2008-04-11 | 527 | Safety Report 2008VX000108 FU2 (Protocol 302) | Russell Katz, MD |
| 615 | 2008-04-11 | 528 | Safety Report 2008VX000737 Initial (Protocol 304) | Russell Katz, MD |
| 616 | 2008-04-14 | 529 | Safety Report 2008VX000750 FU1 (Protocol 108) | Russell Katz, MD |
| 617 | 2008-04-17 | 530 | Safety Report 2007VX002919 FU3 (Protocol 302) | Russell Katz, MD |
| 618 | 2008-04-18 | 531 | Safety Report 2008VX000718 FU1 (Protocol 302) | Russell Katz, MD |
| 619 | 2008-04-22 | 532 | Safety Report 2008VX000727 FU2 (Protocol 108) | Russell Katz, MD |
| 620 | 2008-04-23 | 533 | Safety Report 2008VX000406 FU3 (Protocol 303) | Russell Katz, MD |
| 621 | 2008-04-25 | 534 | Safety Report 2007VX001598 FU2 (Protocol 301) | Russell Katz, MD |
| 622 | 2008-04-30 | 535 | Protocol Amendment: Change in Protocol - VRX-RET-E22-108, Amendment 2 | Russell Katz, MD |
| 623 | 2008-05-05 | 536 | Safety Report 2008VX001003 Initial (Protocol 303) | Russell Katz, MD |
| 624 | 2008-05-09 | Email-FDA | Email to FDA re List of Terms Suicidality Analysis | N. Hershkowitz, FDA; Russell Katz, VPNA |
| 625 | 2008-05-09 | 537 | Gen Corresp Info Amendment QTc Findings Report (Protocol 103) | Russell Katz, MD |

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| | A | B | C | D |
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| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 626 | 2008-05-09 | 538 | Information Amendment: FDA Request for Further Inf. (2008VX000727, Asystole) | Russell Katz, MD |
| 627 | 2008-05-09 | 539 | Protocol Amendment: New Investigator (Protocol 101) | Russell Katz, MD |
| 628 | 2008-05-09 | 540 | Protocol Amendment: New and updated Investigator (Protocol 102) | Russell Katz, MD |
| 629 | 2008-05-09 | 541 | Protocol Amendment: New amd updated Investigator (Protocol 302) | Russell Katz, MD |
| 630 | 2008-05-09 | 542 | Protocol Amendment: New and updated Investigator (Protocol 303) | Russell Katz, MD |
| 631 | 2008-05-09 | 543 | Protocol Amendment: New and updated Investigator (Protocol 304) | Russell Katz, MD |
| 632 | 2008-05-14 | 544 | Safety Report 2008VX000231 FU1 (Protocol 303) | Russell Katz, MD |
| 633 | 2008-05-19 | 545 | Safety Report 2008VX000406 FU4 (Protocol 303) | Russell Katz, MD |
| 634 | 2008-05-19 | 546 | Safety Report 2008VX000750 FU2 (Protocol 108) | Russell Katz, MD |
| 635 | 2008-05-21 | 547 | Safety Report 2008VX001091 Initial (Protocol 304) | Russell Katz, MD |
| 636 | 2008-05-28 | 548 | Safety Report 2008VX000737 FU1 (Protocol 304) | Russell Katz, MD |
| 637 | 2008-06-04 | Tcon-FDA | Tcon Minutes Re Agency request for info in urinary cases 2008VX000406 | Steven Dinsmore MD, FDA Art Rosenthal, VPNA |
| 638 | 2008-06-06 | Email-FDA | Email to FDA re follow-up to Tcon discussion on case number #2008VX000406 | Jackie Ware, FDA; Art Rosenthal, VPNA |
| 639 | 2008-06-11 | Email-FDA | FDA Email re QT Studies Valeant Retigabine IND 53,950 | Beverley Conner, FDA; Art Rosenthal, VPNA |
| 640 | 2008-06-17 | 549 | Safety Report 2008VX001091 FU1 (Protocol 304) | Russell Katz, MD |
| 641 | 2008-06-17 | 550 | Safety Report 2008VX001003 FU1 (Protocol 303) | Russell Katz, MD |
| 642 | 2008-06-19 | 551 | Safety Report 2008VX001296 Initial (Protocol 304) - 7-Day | Russell Katz, MD |
| 643 | 2008-06-25 | 552 | Protocol Amendment: Investigator Updates (Protocol 301 - sites 27 and 33) | Russell Katz, MD |
| 644 | 2008-06-25 | 553 | Protocol Amendment: Investigator Updates (Protocol 303 - sites 27 and 33) | Russell Katz, MD |
| 645 | 2008-06-27 | 554 | Safety Report 2008VX001348 Initial (Protocol 304) - 7-Day | Russell Katz, MD |

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| | A | B | C | D |
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| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 646 | 2008-06-27 | 555 | Safety Report 2008VX001334 Initial (Protocol 304) | Russell Katz, MD |
| 647 | 2008-07-01 | 556 | Safety Report 2008VX001003 FU2 (Protocol 303) | Russell Katz, MD |
| 648 | 2008-07-03 | 557 | General Correspondence: Requesting Review of Proposed Proprietary Name - correction to SN 513 KOTIGA | Russell Katz, MD |
| 649 | 2008-07-03 | 558 | Protocol Amendment - Investigator Update Protocol 302 (sites 504, 507, and 506). | Russell Katz, MD |
| 650 | 2008-07-11 | 559 | Safety Report 2008VX001348 FU1 (Protocol 304) | Russell Katz, MD |
| 651 | 2008-07-14 | 560 | Safety Report 2008VX001296 FU1 (Protocol 304) | Russell Katz, MD |
| 652 | 2008-07-14 | 561 | Safety Report 2008VX001348 FU2 (Protocol 304) | Russell Katz, MD |
| 653 | 2008-07-17 | 562 | Protocol Amendment - Investigator update for protocol VRX-RET-E22-108 | Russell Katz, MD |
| 654 | 2008-07-24 | 563 | Safety Report 2008VX000406 FU5 (Protocol 303) | Russell Katz, MD |
| 655 | 2008-07-30 | 564 | Safety Report 2008VX001157 Initial (Protocol 304) | Russell Katz, MD |
| 656 | 2008-08-11 | 565 | Safety Report 2008VX001157 FU1 (Protocol 304) | Russell Katz, MD |
| 657 | 2008-08-11 | 566 | Safety Report 2008VX001334 FU1 (Protocol 304) | Russell Katz, MD |
| 658 | 2008-08-14 | 567 | Protocol Amendment: New Investigator and Investigator Update for 304 | Russell Katz, MD |
| 659 | 2008-08-15 | 568 | Information Amendment - Unblinded Safety Update (Protocols 301 and 302) | Russell Katz, MD |
| 660 | 2008-08-18 | 569 | Safety Report 2008VX001625 Initial (Protocol 303) | Russell Katz, MD |
| 661 | 2008-08-18 | 570 | Safety Reprot 2008VX001091 FU2 (Protocol 304) | Russell Katz, MD |
| 662 | 2008-08-27 | 571 | New Protocol MR 103 (Amendment 3) | Russell Katz, MD |
| 663 | 2008-08-27 | 572 | Protocol Amendment: Change in Protocol - VRX-RET-E22-303, Amendment 2 | Russell Katz, MD |
| 664 | 2008-08-27 | 573 | Protocol Amendment: Change in Protocol VRX-RET-E22-304, Amendment 2 | Russell Katz, MD |
| 665 | 2008-09-05 | 574 | Protocol Amendment: New Investigators (sites 352, 407, 410, 705, 707, 805, 902, 903) and Investigator Updates (sites 252, 256, 301, 303, 404, 406, 409, 411, 501, 507, 508, 602, 603, 604, 605, 606, 704, 801, 802, 803, 804, 905, 952, 953) for Protocol 302 | Russell Katz, MD |

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| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 666 | 2008-09-12 | 575 | Protocol Amendment: Update Investigators (sites 021 and 025) for Protocol 303 | Russell Katz, MD |
| 667 | 2008-09-15 | 576 | Safety Report 2007VX002663 FU1 (Protocol 303) | Russell Katz, MD |
| 668 | 2008-09-17 | 577 | Safety Report 2008VX001157 FU2 (Protocol 304) | Russell Katz, MD |
| 669 | 2008-09-25 | 578 | Information Amendment: Urinary Retention Case update | Russell Katz, MD |
| 670 | 2008-09-26 | 579 | Safety Report 2008VX001625 FU1 (Protocol 303) | Russell Katz, MD |
| 671 | 2008-10-03 | 580 | Protocol Amendment: New and Update Investigators (update sites 11, 15, 18, 27, 30, 36, 41, 54) (new sites 102, 105, and 106) Protocol 303 | Russell Katz, MD |
| 672 | 2008-10-07 | 581 | Safety Cross Reporting from NP IND for 2008VX001921, Initial (SN 028) | Russell Katz, MD |
| 673 | 2008-10-13 | 582 | Information Amendment - Request for additional information of case 2007VX002955 (Protocol 303) | Russell Katz, MD |
| 674 | 2008-10-17 | 583 | Safety Report 2008VX001973 Initial (Protocol 303) | Russell Katz, MD |
| 675 | 2008-10-22 | 584 | Safety Report 2008VX002060 Initial (Protocol 303) | Russell Katz, MD |
| 676 | 2008-10-29 | 585 | Safety Cross Reporting from NP IND for 2008VX002024, Initial (SN 031) | Russell Katz, MD |
| 677 | 2008-11-12 | 586 | Safety Cross Reporting from NP IND for 2008VX002147, Initial (SN 032) | Russell Katz, MD |
| 678 | 2008-11-17 | 587 | General Correspondence: Requesting Review of Proposed Proprietary Name Change POTIGA | Russell Katz, MD |
| 679 | 2008-11-24 | 588 | Safety Report 2008VX001973 FU1 (Protocol 303) | Russell Katz, MD |
| 680 | 2008-11-25 | 589 | Safety Cross Reporting from NP IND for 2008VX001921, FU1 (SN 034) | Russell Katz, MD |
| 681 | 2008-11-25 | 590 | Safety Cross Reporting from NP IND for 2008VX002024, FU1 (SN 035) | Russell Katz, MD |
| 682 | 2008-11-25 | 591 | Safety Cross Reporting from NP IND for 2008VX002214, Initial (SN 036) | Russell Katz, MD |
| 683 | 2008-12-02 | 592 | Safety Cross Reporting from NP IND for 2008VX002317, Initial (SN 037) | Russell Katz, MD |
| 684 | 2008-12-03 | Email-FDA | FDA Email - Request Additional Info re stroke | Dorothy Demczar, FDA; Art Rosenthal, VPNA |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 685 | 2008-12-15 | 593 | Safety Report 2008VX001973 FU2 (Protocol 303) | Russell Katz, MD |
| 686 | 2008-12-17 | 594 | Safety Cross Reporting from NP IND for 2008VX002214, FU1 (SN 038) | Russell Katz, MD |
| 687 | 2008-12-18 | 595 | Response to FDA email Request info re CVA of 03Dec2008 (Dorothy Demszar) (2006VX002193, 2005VX000651, 2005VX000610 and 2007VX002097) | Russell Katz, MD |
| 688 | 2008-12-19 | 596 | Protocol Amendment - New Investigator and Investigator Updates (Protocol 303) | Russell Katz, MD |
| 689 | 2008-12-19 | 597 | Protocol Amendment - New Investigator and Investigator Updates (Protocol 101) | Russell Katz, MD |
| 690 | 2008-12-19 | 598 | Protocol Amendment - New Investigator (Protocol MR103) | Russell Katz, MD |
| 691 | 2008-12-19 | 599 | Protocol Amendment - New Investigator (Protocol 304) | Russell Katz, MD |
| 692 | 2008-12-23 | 600 | Safety Cross Reporting 2008VX002024 FU2 (SN 039) | Russell Katz, MD |
| 693 | 2008-12-23 | 601 | Safety Cross Reporting 2008VX002582 Initial (SN 040) | Russell Katz, MD |
| 694 | 2008-12-23 | 602 | Safety Cross Reporting 2008VX002147 FU1 (SN 041) | Russell Katz, MD |
| 695 | 2009-01-07 | 603 | Safety Cross Reporting from NP IND for 2008VX002214, FU2 (SN 042) | Russell Katz, MD |
| 696 | 2009-01-07 | 604 | Safety Cross Reporting from NP IND for 2008VX002582, FU1 (SN 043) | Russell Katz, MD |
| 697 | 2009-01-08 | 605 | Information Amendment: SUDEPs | Russell Katz, MD |
| 698 | 2009-01-09 | 606 | General Correspondence - Request for FDA Feedback | Russell Katz, MD |
| 699 | 2009-01-09 | 607 | Protocol Amendment: New Protocol D-23129-3227 for compassionate use | Russell Katz, MD |
| 700 | 2009-01-29 | 608 | Safety Report 2009VX000111 Initial (Protocol 304) | Russell Katz, MD |
| 701 | 2009-02-17 | 609 | Safety Cross Reporting from NP IND for 2008VX001921, FU2 (SN 047) | Russell Katz, MD |
| 702 | 2009-02-17 | 610 | Safety Cross Reporting from NP IND for 2008VX002024, FU3 (SN 048) | Russell Katz, MD |
| 703 | 2009-02-17 | 611 | Safety Cross Reporting from NP IND for 2008VX002147, FU2 (SN 049) | Russell Katz, MD |
| 704 | 2009-02-17 | 612 | Safety Cross Reporting from NP IND for 2008VX002317, FU1 (SN 050) | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 705 | 2009-02-19 | 606-FDA | FDA Email Dorothy Demczar - response to our request for feedback on UTI Renal Aes | D. Demczar, FDA; A. Rosenthal, VPNA |
| 706 | 2009-02-20 | 613 | Safety Cross Reporting from NP IND for 2008VX002582, FU2 (SN 046) | Russell Katz, MD |
| 707 | 2009-02-20 | 614 | Safety Cross Reporting from NP IND for 2008VX002582, FU3 (SN 051) | Russell Katz, MD |
| 708 | 2009-02-20 | 615 | Safety Cross Reporting from NP IND for 2008VX002214, FU3 (SN 052) | Russell Katz, MD |
| 709 | 2009-02-27 | 616 | Information Amendment:– CMC, Nonclinical, Clinical: ZP3 Position Paper | Russell Katz, MD and David Jacobsen-Kram |
| 710 | 2009-03-09 | Email-FDA | FDA Email Dorothy Demczar - Request for info on cardiac events | D. Demczar, FDA; A. Rosenthal, VPNA |
| 711 | 2009-03-10 | Email-FDA | FDA Email Dorothy Demczar - FDA confirmation of Valeant submission of cardiac event information | D. Demczar, FDA; A. Rosenthal, VPNA |
| 712 | 2009-03-12 | 617 | Safety Report 2009VX000341 Protocol 304 | Russell Katz, MD |
| 713 | 2009-03-31 | 618 | Safety Report 2008VX002060 Fu1 Protocol 303 | Russell Katz, MD |
| 714 | 2009-04-03 | 620-FDA | FDA Email Dorothy Demczar - Request for Cardiac Information | D. Demczar, FDA; A. Rosenthal, VPNA |
| 715 | 2009-04-03 | 619 | Protocol Amendment: Investigator Updates - Protocol 303 (sites 3, 14, 21, 36) | Russell Katz, MD |
| 716 | 2009-04-10 | 620 | Response to the Agency's request for further info on cardiac AEs re SN 578 | Russell Katz, MD |
| 717 | 2009-04-10 | 621 | Safety Report 2009VX000551 Protocol 304 | Russell Katz, MD |
| 718 | 2009-04-10 | 622 | Safety Report 2009VX000341 FU 1 Protocol 304 | Russell Katz, MD |
| 719 | 2009-04-24 | 623 | Annual Report 2008 | Russell Katz, MD |
| 720 | 2009-04-30 | 624 | Safety Report 2009VX000111 FU 1 Protocol 304 | Russell Katz, MD |
| 721 | 2009-05-01 | Email-FDA | Email Change in Regulatory Contact and Request for follow-up ZP3 submission of 27-Feb-2009 | D. Demczar, FDA; Sue Hall, VPNA |
| 722 | 2009-05-06 | 625 | General Information - Change in Regulatory Contact | Central Document Room |
| 723 | 2009-05-06 | 626 | Information Amendment - Clinical - IB Supplement 1 April 30 2009 | Russell Katz, MD |
| 724 | 2009-05-06 | 627 | Safety Report 2009VX000341 FU 2 Protocol 304 | Russell Katz, MD |
| 725 | 2009-05-08 | 628 | General Correspondence: Request for Type B Meeting | Russell Katz, MD |

# Retigabine FDA Submission Log for Epilepsy
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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 726 | 2009-05-11 | 628-Email | Email of SN628 to FDA - Valeant Type B, pre-NDA mtg. request | D. Demczar, FDA; N.Hauptmann, VPNA |
| 727 | 2009-05-13 | 629 | Safety Report 2009VX000551 FU 1 Protocol 304 | Russell Katz, MD |
| 728 | 2009-05-14 | 587-FDA | Letter from FDA Regarding Proprietary Name Request - Conditionally Acceptable | Russell Katz, MD |
| 729 | 2009-05-27 | 630 | Safety Report 2009VX000551 FU 2 Protocol 304 | Russell Katz, MD |
| 730 | 2009-05-28 | Email-FDA | FDA Email Change of Primary Regs Contact | D. Demczar, FDA |
| 731 | 2009-05-28 | Email-FDA | FDA Email Approval of Type C meeting request IND 53950 | D. Demczar, FDA; N.Hauptmann, VPNA |
| 732 | 2009-05-28 | Emails-FDA | FDA Multiple Emails Request for copies of 2 Nonclinical Carci study reports | D. Demczar, FDA; Sue Hall, VPNA |
| 733 | 2009-05-28 | 631 | Safety Report 2009VX000914 7-Day Report - Protocol 304 | Russell Katz, MD |
| 734 | 2009-06-08 | 632 | General Correspondence: Response to FDA letter re. SN587 | Russell Katz, MD |
| 735 | 2009-06-08 | 633 | Info Amendment: CMC, Nonclin, Clinial: Addendum to SN616 (ZP3) | Russell Katz, MD |
| 736 | 2009-06-09 | Email-FDA | Email response from Ms. Dorothy Demczar, FDA) regarding ZP3 and additional Pre NDA Type C Meeting & Proposed | D. Demczar |
| 737 | 2009-06-09 | Email-FDA | Email - Request from FDA re: Retigabine Tablets | Beverly Connor, FDA |
| 738 | 2009-06-10 | Note to File | Notes to File - RE FDA correspondence re 09-Mar-2009 cardiac events info | N/A |
| 739 | 2009-06-10 | 634 | Safety Report 2009VX000914 FU 1 7-Day Report Protocol 304 | Russell Katz, MD |
| 740 | 2009-06-10 | 635 | Safety Report 2009VX000551 FU 3 Protocol 304 | Russell Katz, MD |
| 741 | 2009-06-15 | 636 | Safety Report 2009VX000914 FU 2 Protocol 304 | Russell Katz, MD |
| 742 | 2009-06-29 | 637 | Information Amendment - Nonclinical: ZP3 Toxicity (COMET Study) | Russell Katz, MD |
| 743 | 2009-06-30 | 638 | Information Amendment - CMC: ZP3, New Drug Substance Manufacturer (AMRI) | Russell Katz, MD |
| 744 | 2009-07-01 | 639 | Briefing Document for RTG Type C meeting | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 745 | 2009-07-09 | 640 | Protocol Amendment-New Protocol; BE study (RTG113287) | Russell Katz, MD |
| 746 | 2009-07-24 | 641 | Safety Report 2009VX000914 FU3 Protocol 304 | Russell Katz, MD |
| 747 | 2009-07-27 | Email-FDA | FDA Email regarding Questions submitted in briefing package for scheduled FDA Meeting. | Dorothy Demczar |
| 748 | 2009-07-28 | 642 | Information Amendment -Response to Request -Clinical - Analysis report of urinary crystals | Russell Katz, MD |
| 749 | 2009-08-03 | 643 | Information Amendment - CMC (BE Study RTG113287) | Russell Katz, MD |
| 750 | 2009-08-04 | Email-GSK | Email from GSK Type C FDA Meeting Summary | Mark Baumgartner, GSK |
| 751 | 2009-08-05 | 644 | Response to Request for Information: Established Name | Russell Katz, MD |
| 752 | 2009-08-05 | Email-644-FDA | Email to FDA re Retigabine Established Name (Ser. No 644) | D. Demczar, FDA |
| 753 | 2009-08-12 | 645 | Protocol Amendment -New Investigators and Investigator Updates for Protocol 304 (various sites) | Russell Katz, MD |
| 754 | 2009-08-14 | Email-GSK | Email from GSK - Follow up to Type C meeting of Aug 4 2009 - Generic Name Change | Mark Baumgartner, GSK |
| 755 | 2009-08-18 | Email-FDA | Email Response from FDA re Pharma/ Toxicology group Assessment of ZP3. | D. Demczar FDA: Sue Hall, VPNA |
| 756 | 2009-08-19 | Email-FDA | Email to FDA re Approval of Meeting Minutes | D. Demczar FDA: Sue Hall, VPNA |
| 757 | 2009-08-28 | 646 | General Correspondence - Retigabine Generic Name - Request for Teleconference | Russell Katz, MD |
| 758 | 2009-08-28 | Email-FDA | Email to FDA re USAN concerns re Generic Name Change (SN644) | Sue Hall, VPNA; D. Demczar, FDA |
| 759 | 2009-08-31 | 648-FDA | FDA Letter with Meeting Minutes of Aug. 4, 2009 on Retigabine Tablets | Russell Katz, MD |
| 760 | 2009-09-03 | 647 | Protocol Amendment: New Protocol RTG113215 (PI: Hussani) | Russell Katz, MD |
| 761 | 2009-09-15 | 648 | Information Amendment: CMC (BE Study RTG113287) - Container-closure | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date** yyyy-mm-dd | **Ser. No.** | **Description** | **FDA Contact** |
| 762 | 2009-09-15 | 649 | Information Amendment: CMC (MR Infusion Study RTG113215) | Russell Katz, MD |
| 763 | 2009-09-17 | 650 | Safety Report 2009VX000914FU4 Protocol 304 (7-Day Alert) | Russell Katz, MD |
| 764 | 2009-09-21 | Email-GSK | Email from GSK - CMC notes from Pre-NDA discussion re Briefing Package | Mark Baumgartner, GSK |
| 765 | 2009-09-22 | 651 | Safety Report 2009VX000111 FU2 Protocol 304 | Russell Katz, MD |
| 766 | 2009-09-22 | 652 | Safety Report 2009VX001807 (UTI) Protocol 303 | Russell Katz, MD |
| 767 | 2009-09-24 | Email-FDA | Welcome to the FDA User Fee System Email from FDA re user fees. | Ms. Demczar |
| 768 | 2009-09-28 | 653 | Protocol Amendment: New Protocol RTG113214 (Regional GI Absorbsion study) | Russell Katz, MD |
| 769 | 2009-10-05 | 654 | Information Amendment: CMC - RTG113214 Regional Intellasite GI Absorbtion Study | Russell Katz, MD |
| 770 | 2009-10-09 | 655 | General Correspondence - Summary of ZP3 Impurity information submitted | Russell Katz, MD |
| 771 | 2009-10-15 | 656 | Safety Report 2009VX001962 Initial Protocol 303 | Russell Katz, MD |
| 772 | 2009-10-15 | 657 | General Correspondence: Proposed Pediatric Study Request | Russell Katz, MD |
| 773 | 2009-10-19 | Email-FDA | EM: S Hall to Dorothy Demczar Concerns raised by USAN - FDA position | Dorothy Demczar |
| 774 | 2009-10-22 | 658 | Safety Report 2009VX001962 FU1 Protocol 303 | Russell Katz, MD |
| 775 | 2009-10-22 | 659 | Safety Report 2009VX001807 FU1 Protocol 303 | Russell Katz, MD |
| 776 | 2009-10-29 | Email-FDA | EM: Michael Jones, Re: User Fee for Potiga PD3009743 | Michael Jones |
| 777 | 2009-11-02 | 660 | Safety Report 2008VX000406 FU6 Protocol 303 | Russell Katz, MD |
| 778 | 2009-11-06 | 661 | Safety Report 2009VX001807 FU2 Protocol 303 | Russell Katz, MD |
| 779 | 2009-11-06 | 662 | Safety Report 2009VX000111 FU3 Protocol 304 | Russell Katz, MD |
| 780 | 2009-11-25 | 663 | Protocol Amendment - New Investigator and Investigator Updates Protocol 303 | Russell Katz, MD |
| 781 | 2009-11-25 | 664 | Safety Report 2009VX000111 FU4 Protocol 304 | Russell Katz, MD |
| 782 | 2009-12-01 | 665 | Safrety Report 2009VX002241 Prtocol 304 | Russell Katz, MD |
| 783 | 2009-12-11 | 666 | Safety Report 2009VX002256 Initial Protocol 304 | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 784 | 2009-12-11 | 667 | Annual Report 2009 | Russell Katz, MD |
| 785 | 2009-12-21 | 668 | Protocol Amendment - Study 303 - urinanalysis substudy | Russell Katz, MD |
| 786 | 2009-12-21 | 669 | Safety Report 2009VX002241 FU1 Protocol 304 | Russell Katz, MD |
| 787 | 2009-12-21 | Ltr-USAN | Letter to USAN-Request for Change of Adopted Name to Lorvigabine | Stephanie Shubat, USAN |
| 788 | 2009-12-21 | 670 | Safety Report 2009VX002256 FU1 Protocol 304 | Russell Katz, MD |
| 789 | 2010-02-05 | 671 | Safety Report 2009VX002256 FU 2 Protocol 304 | Russell Katz, MD |
| 790 | 2010-02-10 | Ltr-USAN | USAN Letter - Approved Change in Proprietary Name to EZOGAINE | Stephanie Shubat, USAN |
| 791 | 2010-03-16 | 672 | Safety Report 2009VX002015 Initial Protocol 304 | Russell Katz, MD |
| 792 | 2010-03-15 | File Note | **NOTE TO FILE: Change from Paper to All Electronic Regulatory Files to be maintained in Live Link** | Sherron Balkcum |
| 793 | 2010-03-15 | Email | Charity Abelardo sent an email to Stephanie Keefe to follow up on the letter regarding the clinical hold on IND 53,950. Ms. Abelardo asked that the letter be sent to Valeant via email when issued. | Keefe, Stephanie |
| 794 | 2010-03-17 | Email | Stephanie Keefe replied to Charity Abelardo's email stating she would send an electronic copy of the clinical hold letter once it is signed off. Ms. Keefe added that it was in the final stages and that she would notify Ms. Abelardo when it was signed. | Stephanie Keefe |
| 795 | 2010-03-22 | 673 | Safety Report 2009VX001807 FU 3 Protocol 303 | Russell Katz, MD |
| 796 | 2010-03-22 | 674 | CMC Information Amendment, analytical testing site (updated and new), 200 mg tablet, specification and method alignment with NDA. | Russell Katz, MD |
| 797 | 2010-03-30 | 675 | USAN Adopted Name Change from Retigabine to Ezogabine | Russell Katz, MD |
| 798 | 2010-03-31 | 676 | Clinical Information Amendment: Supplment 1 to IB, Protocol Amendment: New Protocol RTG1134137 | Russell Katz, MD |
| 799 | 2010-03-26 | Letter | Letter from FDA: Partial Clinical Hold - PPSR Inadequate | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 800 | 2010-04-07 | Email | Charity Abelardo sent an email to Stephanie Keefe to confirm that the partial clinical hold was to determine if the modified PK study in subjects aged >12 years to 18 years would be acceptable. | Stephanie Keefe |
| 801 | 2010-04-07 | Email | Stephanie Keefe replied to Charity Abelardo's email confirming Valaent's understanding about the partial clinical hold. | Stephanie Keefe |
| 802 | 2010-04-09 | 677 | Information Amendment:CMC: additional strengths of retigabine MR formulation 1 (160 mg, 320 mg, 480 mg, and 640 mg | Russell Katz, MD |
| 803 | 2010-04-29 | 678 | Protocol Amendment: Change in Protocol - 303 & 304 amendment 3 to extend OLE study and Amendment 2 to Protocol RTG113215 | Russell Katz, MD |
| 804 | 2010-05-07 | 679 | Correction to SN 640 (Protocol Amendment: New Protocol RTG113287 [BE Study]. Form 3674 was replaced as the document submitted with SN 640 was incorrect ly marked. Form 1572 for the Principal Investigator was also provided as it was inadvertantly omitted from SN 640. | Russell Katz, MD |
| 805 | 2010-05-13 | 680 | Safety Report 2009VX002015 FU1 Protocol 304 | Russell Katz, MD |
| 806 | 2010-05-13 | 681 | Safety Report 2009VX001807 FU 4 Protocol 303 | Russell Katz, MD |
| 807 | 2010-06-03 | 682 | Safety Report AESI, 2010VX000755 Initial *Gastrointestinal Haemorrhage, Anaemia*, Protocol RTG113215 | Russell Katz, MD |
| 808 | 2010-06-09 | 683 | Information Amendment: Clinical - Notification of discontinuation of study RTG1134137 | Russell Katz, MD |
| 809 | 2010-06-09 | 684 | Safety Report AESI, 2010VV000854 Initial withdrawal due to infection, *Influenza like illnes* s, Protocol RTG1134137 | Russell Katz, MD |
| 810 | 2010-07-07 | 685 | Safety Report AESI, 2010VX000854 FU1 withdrawal due to infection Influenza like illness, Protocol RTG114137, additional information | Russell Katz, MD |

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| | A | B | C | D |
|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 811 | 2010-07-09 | 686 | General Correspondence: Change in Contact Details. Notification of change of contact details for Susan Hall (change in contact details from Aliso Viejo, CA to Durham, NC) | Russell Katz, MD |
| 812 | 2010-08-04 | 687 | Safety Report, 2008VX000406.FU7 Protocol 303` | Russell Katz, MD |
| 813 | 2010-08-21 | 688 | Protocol Amendment - Investigator Updates VRX-RET-E22-303 (note: letter dated 19-Jul-2010) | Russell Katz, MD |
| 814 | 2010-10-04 | 689 | Periodic Safety Report 2010VX000873 Initial Protocol 303 | Russell Katz, MD |
| 815 | 2010-10-04 | 690 | Periodic Safety Report 2010VX001611 Initial Protocol 303 | Russell Katz, MD |
| 816 | 2010-10-06 | 691 | Periodic Safety Report 2010VX001617 Initial Protocol 304 | Russell Katz, MD |
| 817 | 2010-10-13 | 692 | Periodic Safety Report 2010VX001683 Initial Protocol 303 | Russell Katz, MD |
| 818 | 2010-10-15 | 693 | Safety Report 2010VX001617 FU 1 Protocol 303 | Russell Katz, MD |
| 819 | 2010-10-15 | 694 | Safety Report 2010VX001611 FU 1 Protocol 303 | Russell Katz, MD |
| 820 | 2010-10-20 | 695 | Periodic Safety Report 2010VX001683 FU1 Protocol 303 | Russell Katz, MD |
| 821 | 2010-10-20 | 696 | Periodic Safety Report 2010VX001763 Initial Protocol 303 | Russell Katz, MD |
| 822 | 2010-10-25 | 697 | Periodic Safety Report 2010VX001770 Initial Protocol 304 | Russell Katz, MD |
| 823 | 2010-10-26 | 698 | Periodic Safety Report 2010VX001763 FU1 Protocol 303 | Russell Katz, MD |
| 824 | 2010-11-01 | 699 | Protocol Amendment: New Protocol Peds-PK Protocol 1132834. Info Amend: CMC 12 mg and 25 mg strengths | Russell Katz, MD |
| 825 | 2010-11-05 | 700 | Protocol Amendment: New Protocol Peds OLE RTG113388 | Russell Katz, MD |
| 826 | 2010-12-07 | 701 | General Correspondence: Delay of Peds PK and Peds OLE studies (RTG113284 and RTG113388) | Russell Katz, MD |
| 827 | 2010-12-08 | 702 | Safety Report 2010VX001770 FU1 Protocol 304 | Russell Katz, MD |

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|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 828 | 2010-12-13 | 703 | Gen. Corresp - Original (12-10-2011) Letter of Authorization for GSK Cross Reference plus Replacement (Correction of Date) Letter | Russell Katz, MD |
| 829 | 2010-12-21 | 704 | Annual Report October 1, 2009 - September 30, 2010 | Russell Katz, MD |
| 830 | 2010-12-28 | 705 | IND Safety Report Initial 7-day alert 2010VRX002206 Possible Stroke- Protocol 303. Sent via FedEx, email and fax (failed). | Russell Katz, MD |
| 831 | 2011-01-03 | 706 | IND Safety Report FU #2 2010VX001683 Lumbar Radiculapathy (Protocol 303) | Russell Katz, MD |
| 832 | 2011-01-03 | 707 | IND Safety Report Initial 2010VX002169 (Pneumonia) and 2010VX002186 (Neutropenia) Protocol 303 | Russell Katz, MD |
| 833 | 2011-01-05 | 708 | IND Safety Report FU #1 2010VX002206 - Protocol 303. Event term revised to Asphyxia and downgraded to unrelated to study drug | Russell Katz, MD |
| 834 | 2011-01-05 | 709 | IND Safety Report 2010VX002186 FU1. Protocol 303 | Russell Katz, MD |
| 835 | 2011-01-06 | 710 | Protocol Amendment: New Investigator and Investigator Updates Protocol 303 (sites 102, 106, 152, 201, 202, 203, 204, 001, 004, 008, 014, 021, 041, 025) | Russell Katz, MD |
| 836 | 2011-01-07 | 711 | IND Safety Report FU #1 2010VX002169 Pneumonia. Protocol 303 | Russell Katz, MD |
| 837 | 2011-01-26 | 712 | IND Safety Report 2011VX000246 Initial Pneumonia Influenzal. Protocol 304 | Russell Katz, MD |
| 838 | 2011-01-26 | 713 | Protocol Amendment 304: New Investigator and Investigator Updates Protocol 304 | Russell Katz, MD |

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|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 839 | 2011-02-04 | 714 | Protocol Amendment 303: New Investigator and Investigator | Russell Katz, MD |
| 840 | 2011-02-17 | 715 | IND Safety Report FU #2 2010VX001770 Neutropenia Protoc | Russell Katz, MD |
| 841 | 2011-02-28 | 716 | IND Safety Report FU #1 2011VX000246 Pneumonia Protoc | Russell Katz, MD |
| 842 | 2011-03-10 | 717 | Protocol Amendment 304: New Investigator and Investigator | Russell Katz, MD |
| 843 | 2011-03-14 | 718 | IND Safety Report FU #2 2010VX002186 Neutropenia Protocol 303 | Russell Katz, MD |
| 844 | 2011-03-14 | 719 | IND Safety Report FU #2 2011VX000246 Pneumonia Protoc | Russell Katz, MD |
| 845 | 2011-04-05 | 720 | IND Safety Report 2010VX001763 FU2 Protocol 303 | Russell Katz, MD |
| 846 | 2011-04-13 | 721 | IND Safety Report-FU3-2011VX000246 Protocol 304 - AESI (Pheumonia Streptococcal) | Russell Katz, MD |
| 847 | 2011-04-18 | 722 | Protocol Amendment 303 and 304: Investigator Update (Leroy site 025) and (DeDeyn site 304) | Russell Katz, MD |
| 848 | 2011-04-20 | 723 | IND Safety Report - Initial - 2011VX001082 Gastroenteritis Cross Report with GSK IND 111,072 Protocol RTG114552 | Russell Katz, MD |
| 849 | 2011-04-21 | 724 | IND Safety Report FU #3 2010VX002186 Neutropenia Protocol 303 | Russell Katz, MD |
| 850 | 2011-04-27 | 725 | IND Module 3 CMC Information Amendment Report | Russell Katz, MD |
| 851 | 2011-05-06 | 726 | IND Safety Report - 2011VX001082 FU1 Appendicitis and Appendicectomy Cross Report with GSK IND 111,072 Protocol RTG114552 | Russell Katz, MD |
| 852 | 2011-05-011 | email | Follow-up to status of PPSR | Karen Abraham-Burrell |

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|---|---|---|---|---|
| 1 | **Date yyyy-mm-dd** | **Ser. No.** | **Description** | **FDA Contact** |
| 853 | 2011-05-18 | 727 | Protocol Amendment 303 and 304: Investigator Update (303: Chung site 004, DeCerce site 021, DeWolfe - new inv. Site 036, Rosenfield site 009. 304: Berkovic site 251) | Russell Katz, MD |
| 854 | 2011-05-18 | 728 | IND Safety Report -2010VX002169 FU # 2 (Protocol 303) | Russell Katz, MD |
| 855 | 2011-05-18 | 729 | IIND Safety Report 2011VX001082 FU # 2 Appendicitis and Appendicectomy Cross Report with GSK IND 111,072 Protocol RTG114552 | Russell Katz, MD |
| 856 | 2011-05-18 | 730 | Change in Sponsor from Valeant to GSK | Russell Katz, MD |
| 857 | 2011-05-20 | 731 | General Correspondence: Change of Sponsor: Transferring the sponsor of IND from Valeant to GlaxoSmithKline LLC (effective May 18, 2011); Change to eCTD format | Russell Katz, MD |
| 858 | 2011-06-01 | 732 | Information Amendment: Clinical, Safety Mfr. Report No. B0680044A | Russell Katz, MD |
| 859 | 2011-06-09 | FDA Letter | FDA Acknowledgement Letter: Transfer of Ownership Valeant Pharmaceuticals to GlaxoSmithKline, LLC | Ms. Stephanie N. Keefe |
| 860 | 2011-06-30 | Telephone Conversation | General Teleconference: Misc Administrative issues including plans for DSUR / Transfer of Ownership | Ms. Susan B. Daugherty |
| 861 | 2011-07-29 | 733 | Submission of Required Postmarketing Protocol Under 505(o) Draft Study Protocols for PMR Reference Nos: 1781-2, 1781-3, 1781-4, and 1781-5 | Russell G. Katz |
| 862 | 2011-07-29 | GSK E-mail | Notification of submission: draft study protocols for Post marketing Requirements (PMRs) for POTIGA (ezogabine) Tablets | Ms. Stephanie N. Keefe |

| Communication Type | Seq No | Re Line | Date | Attachments? |
|---|---|---|---|---|
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Memorandum | 19-Feb-2008 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Memorandum: User Fee for Potiga - PD3009743 | 28-Oct-2009 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Memorandum | 30-Oct-2009 | No |
| GSK Correspondence | | NDA 022345; POTIGA™ (retigabine) Tablets<br>Original Submission: Field Copy<br>Sequence No: 0000 | 30-Oct-2009 | No |
| FDA FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Comment/Information Request | 04-Nov-2009 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Memorandum | 09-Nov-2009 | No |
| FDA Correspondence | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Acknowledgement | 12-Nov-2009 | No |
| FDA FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Comment/Information Request | 12-Nov-2009 | No |
| FDA FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Comment/Information Request: Information - NDA 022345/Potiga (retigabine) tablets | 12-Nov-2009 | No |

| Communication Type | Seq No | Re Line | Date | Attachments? |
|---|---|---|---|---|
| GSK Correspondence | 0001 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request/Comment: Clinical<br>Sequence No: 0001 | 19-Nov-2009 | No |
| GSK Correspondence | 0002 | NDA 022345; POTIGA™ (retigabine) Tablets<br>General Correspondence: Request For Proprietary Name Review<br>Sequence No: 0002 | 20-Nov-2009 | No |
| GSK Correspondence | 0003 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request/Comment: Efficacy, Statistical: The purpose of this submission is to respond to the Division's request<br>Sequence No: 0003 | 04-Dec-2009 | No |
| GSK Correspondence | 0004 | NDA 022345; POTIGA™ (retigabine) Tablets<br>General Correspondence:This Submission is to clarify that our original NDA included the required certification by inclusion of FDA form 3674<br>Sequence No: 0004 | 08-Dec-2009 | No |
| GSK Correspondence | 0005 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Type C Meeting Request and Background Information; Request for 90-day Conference<br>Sequence No: 0005 | 11-Dec-2009 | No |
| GSK Correspondence | 0006 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request/Comment for Information<br>Protocol Violations for Studies 205, 301 and 302<br>Sequence No: 0006 | 24-Dec-2009 | No |
| GSK Correspondence | 0008 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request for Information Tabulated Urinalysis Data and Case Narratives<br>Sequence No: 0008 | 26-Jan-2010 | No |

| Communication Type | Seq No | Re Line | Date | Attachments? |
|---|---|---|---|---|
| GSK Correspondence | 0010 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request for Information: Request for Clarification<br>Sequence No: 0010 | 12-Feb-2010 | No |
| GSK Correspondence | 0011 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request/Comment: The Purpose of this submission is to respond to the CMC items identified<br>Sequence No: 0011 | 17-Feb-2010 | No |
| GSK Correspondence | 0007 | NDA 022345; POTIGA™ (retigabine) Tablets<br>120-Day Safety Update: Safety<br>Sequence No: 0007 | 26-Feb-2010 | No |
| GSK Correspondence | 0009 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request for Information: Clinical Pharmacology,Labeling,Requied Pediatric<br>Sequence No: 0009 | 01-Mar-2010 | No |
| GSK Correspondence | 0013 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request for Information: Re: Request (communicated via email) from the Divison of Neurology Product's<br>Sequence No: 0013 | 05-Mar-2010 | No |
| GSK Correspondence | 0012 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request for Information: Re: Request of February 16, 2010 and February 24, 2010, communicated via email<br>Sequence No: 0012 | 05-Mar-2010 | No |
| GSK Correspondence | 0014 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Clinical Pharmacology Information: Re: To Provide data supporting Bioequivalence of tablets used in clinical studies.<br>Sequence No: 0014 | 10-Mar-2010 | No |

| Communication Type | Seq No | Re Line | Date | Attachments? |
|---|---|---|---|---|
| GSK Correspondence | 0015 | NDA 022345; POTIGA™ (retigabine) Tablet<br>Clinical Information: Refer to the 120-day Safety Update submitted on February 26, 210<br>Sequence No: 0015 | 12-Mar-2010 | No |
| GSK Correspondence | 0016 | NDA 022345; POTIGA™ (retigabine) Tablets<br>General Correspondence: CMC Information: Re:To Provide Stability updates.<br>Field Copy<br>Sequence No: 0016 | 24-Mar-2010 | No |
| GSK Correspondence | 0017 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Amendment to Pending Application Re: Request for Proprietary Name Review<br>Sequence No: 0017 | 01-Apr-2010 | No |
| GSK Correspondence | 0018 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request Information: Clinical: Re: Respond to the Clinical Pharmacology reviewer<br>Sequence No: 0018 | 09-Apr-2010 | No |
| GSK Correspondence | 0019 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request Information: Re: The Clinical reviewer's request for additional bilirubin laboratory values.<br>Sequence No: 0019 | 09-Apr-2010 | No |
| GSK Correspondence | 0020 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request for Information: Clinical reviewer's request for additional information<br>Sequence No: 0020 | 21-Apr-2010 | No |
| GSK Correspondence | 0021 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request/Comment: Revised Draft Labeling to Reflect Change in Proposed Established Name<br>Sequence No: 0021 | 11-May-2010 | No |

| Communication Type | Seq No | Re Line | Date | Attachments? |
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| GSK Correspondence | 0022 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Response to FDA Request for Informationt: Clinical: Response to Request from Clinical Reviewer<br>Sequence No: 0022 | 14-May-2010 | No |
| GSK Correspondence | 0023 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Amendment to Pending Application: Nonclinical: Correction to Previously Submitted Information<br>Sequence No: 0023 | 20-May-2010 | No |
| GSK Correspondence | 0024 | NDA 022345; POTIGA™ (retigabine) Tablets<br>Amendment to Pending Application: Re: The Agency's letter dated May 3, 2010<br>Response to FDA Request/Comment: BA/BE, CMC<br>Sequence No: 0024 | 04-Jun-2010 | No |
| GSK Correspondence | 0025 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to FDA Request/Comment: CMC: Re: The Agency's letter dated May 28, 2010<br>Sequence No: 0025<br>Field Copy | 21-Jun-2010 | No |
| GSK Correspondence | 0026 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to FDA Request/Comment: Clinical: Re: Response to FDA's letter dated May 28, 2010<br>Sequence No: 0026 | 06-Jul-2010 | No |
| GSK Correspondence | 0027 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Correspondence: Change in Contact Details<br>Sequence No: 0027 | 09-Jul-2010 | No |
| GSK Correspondence | 0029 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Correspondence: Advisory Committee Meeting Briefing<br>Sequence No: 0029 | 19-Jul-2010 | No |

| Communication Type | Seq No | Re Line | Date | Attachments? |
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| GSK Correspondence | 0028 | NDA 022345; POTIGA™ (ezogabine) Tablet<br>Response to FDA Request/Comment: CMC: Reference is made to the Agency dated June 25, 2010<br>Sequence No: 0028<br>Field Copy | 20-Jul-2010 | No |
| GSK Correspondence | 0031 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to Request Information : Labeling: Re: The Agency's letter dated July 13, 2010<br>Sequence No: 0031 | 26-Jul-2010 | No |
| GSK Correspondence | 0030 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to Request for Information: Re: Provide formal response to the July 8, 2010<br>Sequence No: 0030 | 29-Jul-2010 | No |
| GSK Correspondence | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>GSK Response to FDA 483 for Retigabine Bioequivalence Study RTG113287 | 04-Aug-2010 | No |
| GSK Correspondence | 0032 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Proposed REMS: Re: Medication Guide and Communication Plan.<br>Sequence No: 0032 | 26-Aug-2010 | No |
| GSK Correspondence | 0033 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Correspondence: Re: Teleconference Meeting Minutes<br>Sequence No: 0033 | 27-Aug-2010 | No |
| GSK Correspondence | 0034 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Amendment to Pending Application: Re: Container Label Changes<br>Sequence No: 0034 | 08-Oct-2010 | No |
| GSK Correspondence | 0035 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to FDA Request Information Amendment: CMC: Re: The Agency's letter dated August 16, 2010 | 18-Oct-2010 | No |

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| | | Sequence No: 0035<br>Field Copy | | |
| GSK Correspondence | 0036 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Amendment to Pending Application: Re: The discussion and agreements made during the telecon. of Oct. 18, 2010<br>Response to FDA Request/Comment: Re: To outline the measures that have been take to lower ZP3 level<br>Se | 20-Oct-2010 | No |
| GSK Correspondence | 0037 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to FDA Request/Comment: Re: Response is provided in m1.11.3<br>Sequence No: 0037 | 22-Oct-2010 | No |
| GSK Correspondence | 0038 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to FDA Request/Comment: Re:That the Division accept a revised ZP3<br>Sequence No: 0038 | 15-Nov-2010 | No |
| GSK Correspondence | 0039 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Amendment to Pending Application: Re: Response to the request for additional information<br>Sequence No: 0039 | 17-Nov-2010 | No |
| GSK Correspondence | 0040 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Correspondence: Letter of Authorization<br>Sequence No: 0040<br><br>IND 053950; Potiga™ (ezogabine) Tablets<br>General Correspondence: To grant permission for future cross-reference of IND<br>Serial No.: 0703 | 13-Dec-2010 | No |
| GSK Correspondence | 0042 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Amendment to Pending Application: Resubmission of Labeling<br>Response to FDA Request/Comment: Amendment to the Request for Proprietary Name Review<br>Sequence No: 0042 | 21-Apr-2011 | No |

| Communication Type | Seq No | Re Line | Date | Attachments? |
|---|---|---|---|---|
| GSK Correspondence | 0043 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Amendment to Pending Application: Medication Guide and Communication Plan<br>Sequence No: 0043 | 01-Jun-2011 | No |
| GSK Correspondence | 0044 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Proposed REMS to address the comments received on June 1.<br>Sequence No: 0044 | 06-Jun-2011 | No |
| GSK Correspondence | 0045 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Proposed REMS: To accept and implement the changes requested on June 8, 2011 and June 9, 2011<br>Sequence No: 0045 | 10-Jun-2011 | No |
| GSK Correspondence | 0047 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Amendment to Pending Application<br>Response to request for revision to proposed Labeling<br>Sequence No: 0047 | 10-Jun-2011 | No |
| GSK Correspondence | 0046 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Amendment to Pending Application: Proposed Labeling and Carton/Container Labeling<br>Sequence No: 0046 | 10-Jun-2011 | No |
| GSK Correspondence | 0048 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Correspondence: Other: Change in Application Owner<br>Sequence No: 0048 | 22-Jun-2011 | No |
| GSK Correspondence | 0049 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Correspondence: Change In Ownership of the Application<br>Sequence No: 0049 | 23-Jun-2011 | No |

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|---|---|---|---|---|
| GSK Correspondence | | 015-Day ADR Report | 29-Jun-2011 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to FDA Request/Comment: Response to FDA Request for Change to PREA PMR | 29-Jun-2011 | No |
| FDA FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Comment/Information Request: Proposed Change to PREA PMR | 29-Jun-2011 | No |
| GSK Telephone Conversation | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Teleconference: Plans for Labeling Supplement and REMS Modification; misc. administrative issues | 30-Jun-2011 | No |
| GSK Correspondence | | 015-Day ADR Report | 01-Jul-2011 | No |
| FDA Correspondence | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Acknowledgement: NEW POSTMARKETING REQUIREMENTS | 01-Jul-2011 | No |
| GSK Correspondence | | 015-Day ADR Report | 08-Jul-2011 | No |
| GSK Correspondence | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Correspondence: Advertising/Promotion<br>REQUEST FOR ADVISORY COMMENTS: CONSUMER CORE LAUNCH MATERIALS | 08-Jul-2011 | No |
| GSK Correspondence | | NDA 020031; PAXIL® (paroxetine hydrochloride) Tablets<br>NDA 018473; VENTOLIN® (albuterol, USP) Inhalation Aerosol<br>NDA 018603; ZOVIRAX® (acyclovir sodium) for Injection<br>NDA 018644; WELLBUTRIN® (bupropion hydrochloride) Tablets<br>NDA 020121; FLONASE® (fluti | 11-Jul-2011 | No |

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| GSK Correspondence | 0051 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Correspondence: TIME SENSITIVE PATENT INFORMATION<br>Sequence No: 0051 | 11-Jul-2011 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Memorandum: Advertising/Promotion | 12-Jul-2011 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Memorandum: Notification of Submission | 13-Jul-2011 | No |
| GSK Correspondence | 0050 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>NEW SUPPLEMENT PROPOSED REMS MODIFICATION LABELING CHANGES<br>Sequence No: 0050 | 13-Jul-2011 | No |
| FDA Correspondence | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Comment/Information Request: Advertising/Promotion | 18-Jul-2011 | No |
| FDA FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Comment/Information Request: REMS Modification | 18-Jul-2011 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to FDA Request/Comment: REMS Modification | 18-Jul-2011 | No |
| FDA FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Comment/Information Request: REMS modification; required language for cover letter | 18-Jul-2011 | No |

| Communication Type | Seq No | Re Line | Date | Attachments? |
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| GSK Correspondence | 0052 | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Amendment to Pending NDA Supplement PROPOSED REMS MODIFICATION LABELING CHANGES<br>Sequence No: 0052 | 19-Jul-2011 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>Response to FDA Request/Comment: Follow up regarding submission to address FDA request for information on REMS | 27-Jul-2011 | No |
| FDA FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Memorandum: Acknowledgement of response to FDA request for information associated with REMS modification | 29-Jul-2011 | No |
| GSK FAX/E-mail | | NDA 022345; POTIGA™ (ezogabine) Tablets<br>General Memorandum: Notification of PMR draft protocol submission | 29-Jul-2011 | No |
| GSK Correspondence | 0053 | IND 053950; Potiga™ (ezogabine) Tablets<br>Required Postmarketing Protocol Under 505(o)<br>Draft Study Protocols for PMR Reference Nos: 1781-2, 1781-3, 1781-4, and 1781-5<br>Serial No.: 0733<br>Sequence No.: 0733<br><br>NDA 022345; POTIGA™ (ezogabine) Tablets<br>Requir | 29-Jul-2011 | No |